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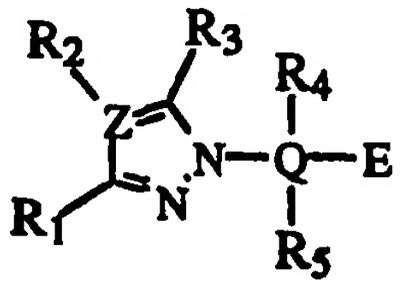
(54) Title: PYRAZOLE INHIBITORS OF CYTOKINE PRODUCTION

(57) Abstract

Compounds having formula (I) are useful for treating diseases that are prevented by or ameliorated with Interleukin–2, Interleukin–4, or Interleukin–5 production inhibitors.



(I)

PYRAZOLE INHIBITORS OF CYTOKINE PRODUCTION

Technical Field

The present invention relates to organic compounds and compositions that are cytokine synthesis inhibitors, processes for making such compounds, synthetic intermediates employed in these processes, and methods for inhibiting cytokine production in a mammal.

Background of The Invention

Therapeutic control of the immune system is the goal of many approaches toward the treatment of autoimmune diseases that differ in organ specific involvement, pathogenic cofactors, response to treatment and prognosis. They range from diseases with "spontaneous" onset such as rheumatoid arthritis to rejection reactions after allograft organ transplantation.

Interleukin 2 (IL-2), a lymphokine produced by activated T-cells, is a key regulator of immune and inflammatory responses. It promotes T cell proliferation *in vitro* and differentiation of B cells, activated macrophages, NK cells and LAK cells. The central importance of IL-2 in initiating adaptive immune responses such as the rejection of tissue grafts is well-illustrated by drugs that are most commonly used to suppress undesirable effects such as the rejection of tissue grafts. The drugs cyclosporin A and FK506 inhibit IL-2 production by disrupting signalling initiated through the T-cell receptor. The drug rapamycin also inhibits signalling through the T cell receptor. Cyclosporin A and rapamycin act synergistically to inhibit immune responses by preventing the IL-2 driven clonal expansion of T cells (Brazelton and Morris, Current Opinion in Immunology 8, 710 (1996)).

Compounds of this invention, due to their ability to inhibit IL-2 production, can be anticipated to demonstrate therapeutic efficacy in disease states where IL-2 is a key orchestrator of the immune response such as rheumatoid arthritis, atopic dermatitis, psoriasis and the rejection of tissue grafts.

Increased local elaboration of the Th2-type cytokines Interleukin-5 (IL-5) and Interleukin-4 (IL-4) has clearly been implicated in the pathogenesis of atopic asthma (Am. J.Respir. Crit. Care Med. 154, 1497 (1996)). IL-5 has selective biologic effects on eosinophils and their precursors and may regulate selective accumulation of these cells in the asthmatic

(vi) $-N_3$,

(e) a carboxy protecting group,

(f) alkyl of one to fifteen carbons,

(g) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkoxy of one to fifteen carbons,

(ii) thioalkoxy of one to fifteen carbons,

(iii) aryl,

(iv) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(v) cycloalkyl of three to twelve carbons, and

(vi) halo,

(h) alkenyl of three to fifteen carbons,
provided that a carbon of a carbon-carbon double bond is not attached directly to oxygen,

(i) alkynyl of three to fifteen carbons,
provided that a carbon of a carbon-carbon triple bond is not attached directly to oxygen, and

(j) cycloalkyl of three to twelve carbons,

(10) $-L_1NR_7R_8$ where L_1 is selected from

(a) a covalent bond,

(b) -X'C(X)- where X and X' are independently O or S,

(c) -C(X)-, and

(d) $-NR_6-$ and

R_7 and R_8 are independently selected from

(a) hydrogen,

(b) alkanoyl where the alkyl part is one to fifteen carbons,

(c) alkoxycarbonyl where the alkyl part is one to fifteen carbons,

(l) alkenyl of three to fifteen carbons,
provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,
(m) alkynyl of three to fifteen carbons,
provided that a carbon of a carbon-carbon triple bond is not attached directly to nitrogen,
(n) $-SO_2$-alkyl, and
(o) cycloalkyl of three to twelve carbons, or

R_7 and R_8 together with the nitrogen atom to which they are attached form a ring selected from
(i) aziridine,
(ii) azetidine,
(iii) pyrrolidine,
(iv) piperidine,
(v) piperazine,
(vi) morpholine,
(vii) thiomorpholine, and
(viii) thiomorpholine sulfone
where (i)-(viii) can be optionally substituted with 1, 2, or 3 substituents selected from the group consisting of alkyl of one to fifteen carbons,

(11) $-L_2R_9$ where L_2 is selected from
(a) $-L_1-$,
(b) -O-, and
(c) $-S(O)_t-$ where t is 0, 1, or 2 and

R_9 is selected from
(a) cycloalkyl of three to twelve carbons,
(b) aryl
(c) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
(i) alkyl of one to fifteen carbons,
(ii) alkoxy of one to fifteen carbons,
(iii) thioalkoxy of one to fifteen carbons,
(iv) halo,

halo,
$-NO_2$, and
$-N_3$,

(12) alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 halo substituents,

(13) alkyl of one to fifteen carbons,

(14) alkenyl of two to fifteen carbons,

(15) alkynyl of two to fifteen carbons

where (13)-(15) can be optionally substituted with

(a) (=X),

(b) alkanoyloxy where the alkyl part is one to fifteen carbons,

(c) alkoxy of one to fifteen carbons,

(d) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(e) thioalkoxy of one to fifteen carbons,

(f) perfluoroalkoxy of one to fifteen carbons,

(g) $-N_3$,

(h) $-NO_2$,

(i) -CN,

(j) -OH,

(k) -OG

(l) cycloalkyl of three to twelve carbons,

(m) halo,

(n) $-CO_2R_6$,

(o) $-L_1NR_7R_8$, and

(p) $-L_2R_9$,

(16) $-L_2$-heterocycle, and

(17) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3 or 4 substituents independently selected from

(a) alkyl of one to fifteen carbons,

(b) perfluoroalkyl of one to fifteen carbons,

(c) alkoxy of one to fifteen carbons,

(d) thioalkoxy of one to fifteen carbons,

(e) halo, and

(f) $-NO_2$,

(v) thiomorpholine sulfone

(6) perfluoroalkyl of one to fifteen carbons,

(7) cycloalkyl of three to ten carbons,

(8) alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group constsing of halo,

(9) alkyl of one to fifteen carbons substituted with

(a) -CN,

(b) -OH,

provided that no two -OH groups are attached to the same carbon,

(c) (=X), and

(d) $-CO_2R_6$, and

(10) halogen;

provided that when X is nitrogen, R_2 is absent;

Q is aryl or heterocycle where, when Q is phenyl, the phenyl is 2-, 3-, or 4- substituted by E relative to the position of attachment of the pyrazole or 1,2,4-triazole ring to the phenyl ring;

$\mathbf{R_4}$ and $\mathbf{R_5}$ are independently selected from

(1) hydrogen,

(2) alkyl of one to fifteen carbons,

(3) alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 halo substituents,

(4) alkyl of one to fifteen carbons substituted with

(a) -CN,

(b) $-CO_2R_6$,

(c) $-L_1NR_7R_8$, and

(d) $-L_2R_9$,

(5) perfluoroalkyl of one to fifteen carbons,

(6) -CN,

(7) $-CO_2R_6$,

(8) $-L_1NR_7R_8$,

(9) $-L_2R_9$,

(10) alkoxy of one to fifteen carbons,

(11) thioalkoxy of one to fifteen carbons,

(g) $-N(R_7)C(O)N(R_8)-$,
(h) $-N(R_7)SO_2N(R_8)-$,
(i) -X-,
(j) $-(CH_2)_mO-$,
(k) $-O(CH_2)_m-$,
(l) $-N(R_7)C(X)-$,
(m) $-C(X)N(R_7)-$,
(n) $-S(O)_t(CH_2)_m-$,
(o) $-(CH_2)_mS(O)_t-$,
(p) $-NR_7(CH_2)_m-$,
(q) $-(CH_2)_mNR_7-$,
(r) $-NR_7S(O)_t-$,
(s) $-S(O)_tNR_7-$,
(t) -N=C(H)-,
(u) -C(H)=N-,
(v) -ON=CH-,
(w) -CH=NO-

where (g)-(w) are drawn with their left ends attached to Q,

(x) $-N(R_7)C(O)N(R_{10})(R_{11})-$ where R_{10} and R_{11} together with the nitrogen atom to which they are attached form a ring selected from

(i) morpholine,
(ii) thiomorpholine,
(iii) thiomorpholine sulfone, and
(iv) piperidine

where (i)-(iv) are attached to Q through the nitrogen to which is attached R_7 and to B through a carbon in the ring,

(y) $-N(R_7)SO_2N(R_{10})(R_{11})-$, and
(z) $-N(R_7)C(O)N(R_{10})(R_{11})-$ and

B is selected from

(a) alkyl of one to fifteen carbons,
(b) alkenyl of three to fifteen carbons in the E or Z configuration,

provided that a carbon of a carbon-carbon double bond is not directly attached to L_3 when L_3 is other than a covalent bond,

(c) alkynyl of three to fifteen carbons,

alkanoyloxy where the alkyl part is one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
alkoxy of one to fifteen carbons substituted with 1, 2, 3,4, or 5 halo substituents,
perfluoroalkoxy of one to fifteen carbons,
$-N_3$,
$-NO_2$,
-CN,
-OH,
provided that no two -OH groups are attached to the same carbon,
-OG,
cycloalkyl of three to fifteen carbons,
halo,
$-CO_2R_6$,
$-L_1NR_7R_8$, and
$-L_2R_9$,
$-L_2$-heterocycle, and
$-L_2$-heterocycle where the heterocycle is substituted with
1, 2, 3, or 4 substituents independently selected from
alkyl of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NR_XC(O)NR_YR_Z$,
$-C(=NRX)R_YR_Z$,
$-NO_2$, and
$-N_3$,

(ii) (=X)

-CN,
-OH,
provided that no two -OH groups are attached to the same carbon,
-OG,
cycloalkyl of three to fifteen carbons,
halo,
$-CO_2R_6$,
$-L_1NR_7R_8$, and
$-L_2R_9$,

(d) cycloalkyl of three to twelve carbons,

(e) cycloalkenyl of four to twelve carbons,
provided that a carbon of a carbon-carbon-double bond is not attached directly to L_3 when L_3 is other than a covalent bond

where (d) and (e) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkyl of one to fifteen carbons,

(ii) aryl,

(iii) alkoxy of one to fifteen carbons,

(iv) thioalkoxy of one to fifteen carbons,

(v) halo,

(vi) -OH,
provided that no two -OH groups are attached to the same carbon,

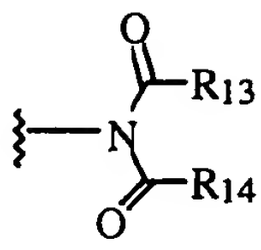
(vii) oxo,

(viii) perfluoroalkyl,

(ix) heterocycle, and

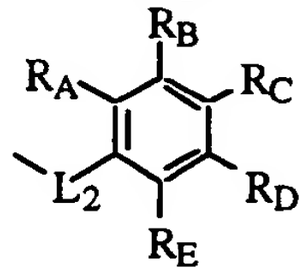
(x) heterocycle substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,

(xvi) halo,
(xvii) $-CO_2R_6$,
(xviii) alkyl optionally substituted with -OH,
(xix) $-L_1NR_7R_8$, and
(xx) $-L_2R_9$, and

(2)  where R_{13} and R_{14} are independently selected from

(a) hydrogen,
(b) alkyl of one to fifteen carbons,
(c) alkenyl of three to fifteen carbons in the E or Z configuration,
provided that a carbon of a carbon-carbon double bond is not attached directly to the C(=O) group,
(d) alkynyl of three to fifteen carbons,
provided that a a carbon-carbon triple bond is not directly attached to the C(=O) group

where (b), (c), and (d) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(i) 
(ii) (=X),
(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,
(iv) alkoxy of one to fifteen carbons,
(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,
(vi) thioalkoxy of one to fifteen carbons,
(vii) perfluoroalkoxy of one to fifteen carbons,
(viii) $-N_3$,
(ix) $-NO_2$,
(x) -CN,
(xi) -OH,

(f) cycloalkenyl of four to twelve carbons,
provided that a carbon of a carbon-carbon double bond is not attached directly to the C(=O) group

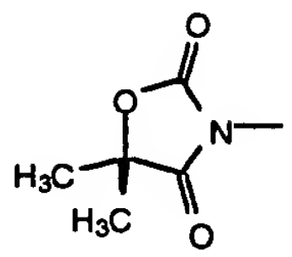
where (e) and (f) can be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from

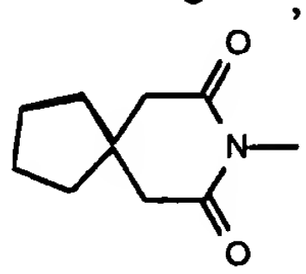
(i) alkyl of one to fifteen carbons,
(ii) aryl,
(iii) alkoxy of one to fifteen carbons,
(iv) thioalkoxy of one to fifteen carbons,
(v) halo,
(vi) -OH,
provided that no two -OH groups are attached to the same carbon,
(vii) heterocycle, and
(viii) heterocycle substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

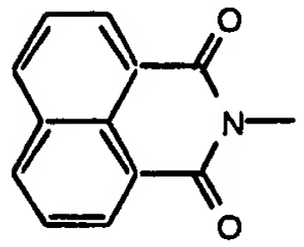
(g) heterocycle, and

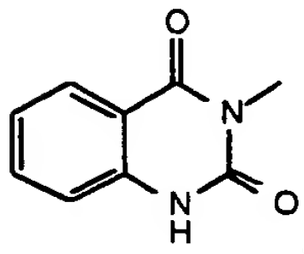
(h) heterocycle substituted with 1, 2, 3, or 4 substituents independently selected from

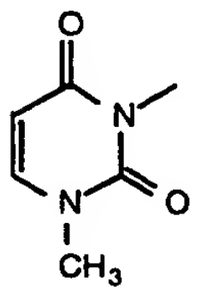
(i) (=X),
(ii) alkanoyl where the alkyl part is one to fifteen carbons,
(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,
(iv) alkoxy of one to fifteen carbons,
(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(i)  ,

(j)  ,

(k)  ,

(l)  , and

(m) 

where (a)-(m) can be optionally substituted with 1, 2, 3, 4, or 5 substituents selected from

halo and

$-L_2R_9$.

In another embodiment, the present invention also relates to a method of inhibiting Interleukin-2, Interleukin-4, and Interleukin-5 production in a mammal comprising administering a therapeutically effective amount of a compound of Formula **I**.

In yet another embodiment, the present invention also relates to a method of treating immunologically-mediated diseases in a mammal comprising administering a therapeutically effective amount of a compound of Formula **I**.

In still yet another embodiment, the present invention relates to pharmaceutical compositions which comprise a therapeutically effective amount of a compound of Formula **I** in combination with a pharmaceutically acceptable carrier.

Compounds of the invention include but are not limited to

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopropanecarboxamide,

2-benzoyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

3a(S)-(3aα,4β,6aα)-N-[4–[3,5–bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]hexahydro-2-oxo-1H-thieno[3,4-d]imidazole-4-pentanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-iodobenzamide,

exo-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]bicyclo[2.2.1]hept-5-ene-2-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methylcyclohexane-carboxamide,

phenylmethyl [1-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-carbonyl]propyl]carbamate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyclohexene-1-carboxamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-fluorophenyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-fluorophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-[4-(trifluoromethyl)-phenyl]urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3,5-dimethylphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methylcyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-phenylurea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-chloro-2-methylphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-[4-(butyloxyphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-methyl-3-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-chloro-4-nitrophenyl)urea,

N-(4-acetylphenyl)-N'-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-n'-(4-methyl-2-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-2-thiophene-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenylcyclopropane-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-iodobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloropropanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-ethylhexanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-hydroxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(hexyloxy)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methylbenzamide,

2-(acetyloxy)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-bromo-2-methylphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4,6-trimethylbenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-chloro-3-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-N-methylbenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-nitro-N-methylbenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chlorobenzenemethanamine,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-5-nitro-1H-pyrazole-4-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluorobenzenemethanamine,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-bromobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(dimethylamino)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(dimethylamino)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chlorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-nitrobenzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-fluorophenyl)benzenemethanamine,

3-[4-[[[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methylbenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(trifluoromethyl)benzamide,
3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile,
methyl 3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoate,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chlorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-thiophenecarboxamide,
(E)-3-[2-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]ethenyl]benzonitrile,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,4-benzenedicarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,5-dinitrobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-difluorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-nitrobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyanobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,3-benzenedicarboxamide,
(Z)-3-[2-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]ethenyl]benzonitrile,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-nitrobenzamide,
3-(aminosulfonyl)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,
methyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoate,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxybenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-bromobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methoxybenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-fluorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-bromobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,3-benzodioxole-5-carboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-3-pyridinecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-3-pyridinecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-6-methyl-3-pyridine-carboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-γ-oxobenzenebutanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chloro-2-methoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methyl-4-(2-thienyl-carbonyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methyl-4-(2-thienyl carbonyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxy-4-(methythio)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-hydroxy-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,4-dihydroxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-hydroxy-6-methoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-bis(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-4-isoxazolecarboxamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-chlorophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(3-cyanophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,4-difluorophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-cyanophenyl)benzamide,

N-[4-[5-[3,5-dimethyl-1H-1,2,4-triazol-1-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-isoxazolecarboxamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-nitrophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,6-difluorophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-bromophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-cyanophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-pyridinyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-(trifluoromethyl)benzamide,

N-[2-(aminocarbonyl)phenyl]-4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]benzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chlorobenzeneacetamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-dichlorobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-5-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-nitrobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chloro-2,5-difluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,4-trifluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,4,5-trifluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4,5-trifluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4,6-trifluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluoro-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,5-trifluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-dichloro-6-fluorobenzamide,

N-4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl-2,4-dichloro-3,5-dinitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,5,6-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,4,5-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-bromo-2,3,5,6-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-2-nitrobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-thiophenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyrrolidinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-3-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-pyridinecarboxamide,

1,1-dimethylethyl 2-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]-1-pyrrolidinecarboxylate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-nitro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5,6-dichloro-3-pyridinecarboxamide

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-4-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-dichloro-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4-chlorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-fluorophenyl]-2,4-difluorobenzamide,

N-[2,4-bis[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-difluorobenzamide,

methyl 2-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-5-[(5-bromo-2-chlorobenzoyl)amino]benzoate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-3,5-dimethyl-4-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-chlorophenyl]-3,5-dimethyl-4-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-(trifluoromethyl)phenyl]-3,5-dimethyl-4-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-methylphenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-methoxyphenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

4-chloro-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-methyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide,

3,5-dimethyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-isoxazolecarboxamide,

4-chloro-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]benzamide,

4-methyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-1,2,3-thiadiazole-5-carboxamide,

3,5-dimethyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-4-isoxazolecarboxamide,

3-fluoro-N-(4-(5-(2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

2-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,

N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

2-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide,

2-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide,

N-(4-(5-ethoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

3-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

3-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

2-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

3-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)phenyl)-3-fluoroisonicotinamide,

3-fluoro-N-(4-(5-(1-methyl-1H-pyrrol-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-chloro-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-(4-(5-chloro-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-cyano-3-tetrahydro-2-furanyl-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-(difluoromethoxy)-3-(1-methyl-1H-pyrrol-3-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-(difluoromethoxy)-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide, and

N-(4-(5-(difluoromethoxy)-3-(1-methyl-1H-pyrrol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide.

Detailed Description of the Invention

Definition of Terms

The term "alkanoyl" refers to an alkyl group attached to the parent molecular group through a carbonyl group.

The term "alkanoyloxy" refers to an alkanoyl group attached to the parent molecular group through an oxygen atom.

The term "alkenyl" refers to a monovalent straight or branched chain group derived from a hydrocarbon of two to fifteen carbons having at least one carbon-carbon double bond. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" refers to a divalent straight or branched chain group derived from a hydrocarbon of two to fifteen carbons having at least one carbon-carbon double bond.

The term "alkoxy" refers to an alkyl group attached to the parent molecular group through an oxygen atom.

The term "alkyl" refers to a monovalent straight or branched chain group derived from an saturated hydrocarbon of one to fifteen carbons. The alkyl groups of this invention can be optionally substituted.

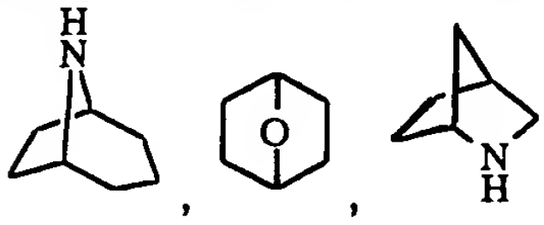
The term "alkylene" refers to a divalent group derived from a straight or branched chain saturated hydrocarbon of one to fifteen carbons.

The term "alkynyl" refers to a monovalent straight or branched chain group derived from a hydrocarbon of one to fifteen carbons having at least one carbon-carbon triple bond. The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" refers to a divalent group derived from a straight or branched

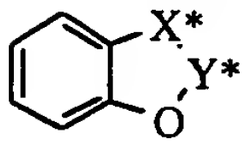
"heterocycle" also includes bicyclic, tricyclic, and tetracyclic groups in which a heterocyclic ring is fused to one or two rings selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles of this type can be attached through the ring to which they are fused or through the heterocyclic ring itself. Heterocycles include, but are not limited to, acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

Heterocyclics also include bridged bicyclic groups where a monocyclic heterocyclic group is bridged by an alkylene group such as



, and the like.

Heterocyclics also include compounds of the formula



where X* is selected from $-CH_2-$, $-CH_2O-$ and -O-,and Y* is selected from -C(O)- and $-(C(R")_2)_v-$, where R" is hydrogen or alkyl of one to four carbons and v is 1, 2, or 3. The heterocycles of this invention can be optionally substituted.

The term "hydroxyl" refers to -OH.

The term "hydroxyl protecting group" refers to a protecting ester or ether group typically employed to block or protect the hydroxyl group while reactions involving other functional sites of the compound are performed. Hydroxyl protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)).

Ther term "perfluoroalkyl" refers to an alkyl group wherein all of the hydrogens have been substituted with fluorides.

The term "pharmaceutically acceptable prodrugs" refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower mammals without undue

Cell and Culture Conditions

Human peripheral blood mononuclear cells were cultured in RPMI 1640 medium supplemented with 10 µg/ml gentamicin, 50 µM 2-mercaptoethanol, 1X MEM non-essential amino acids (Sigma Chemical Co., St. Louis, MO), 100 U/ml sodium penicillin G, 100 µg/ml streptomycin sulfate, 2 mM L-glutamine, 1 mM sodium pyruvate (Life Technologies, Grand Island, NY) and 10% fetal bovine serum (Hyclone, Logan, UT) at 37 ^{o}C with 5% CO_2.

Preparation of Human Peripheral Blood Mononuclear Cells

The procedure in Current Protocols in Immunology, Volume 1, Published by the Greene Publishing Associates and John Wiley & Sons, Inc, Edited by Richard Coico, 1994, hereby incorporated by reference, was followed. Briefly, 50 ml of blood from human volunteers was collected in heparinized syringes and mixed. Blood was diluted 1:1 in Dulbecco's phosphate buffered saline (D-PBS) (Life Technologies, Grand Island, NY) and mixed. PBS-blood mixture was overlaid into 50 ml centrifuge tubes containing 15 ml Histopaque 1077 (Sigma Chemical Co., St. Louis, MO) and centrifuged at 500 X G for 30 minutes at room temperature. Cells at the interface from each Histopaque tube were removed and mixed with 5 ml of D-PBS. Each cell suspension was diluted to 50 ml with D-PBS, mixed and centrifuged at 400 X G for 15 minutes at room temperature. After most of the supernatant was removed, cells were resuspended to 40 ml with D-PBS per tube (2 tubes per donor). Cells were centrifuged at 400 X G for 10 minutes at room temperature. Pellets were resuspended in 10 ml of supplemented RPMI 1640 and cell number determined with a Coulter counter. Cells were diluted to a concentration of 0.5 X 10^6 cells per mL.

Human Concanavalin-A Proliferation Assay (Con HU Assay)

The procedure in Current Protocols in Immunology, Volume 1, Published by the Greene Publishing Associates and John Wiley & Sons, Inc, Edited by Richard Coico, 1994, hereby incorporated by reference, was followed. Briefly, test compounds were added to appropriate wells on 96-well tissue culture plates (Corning Glass Works, Corning, NY) in 20 µl of supplemented RPMI 1640. Human peripheral blood mononuclear cells were added to each well in 100 µl volumes (final cell concentration equal to 50,000 cells per well). After 15 minutes, 100 µl of 5 µg/ml concanavalin-A (Sigma Chemical Co., St. Louis, MO) in supplemented RPMI 1640 was added to a final concentration of 2.5 µg/ml. Plates were incubated for 3 days at 37^{o} C with 5% CO_2. On day 3, plates were pulsed with 0.5 µCi/well tritiated thymidine (New England Nuclear, Boston, MA). After 6 hours, plates were harvested

25	100 (10)	396
26	24 (1)	-
27	100 (10)	299
28	12 (1)	-
29	100 (10)	51
30	6 (1)	-
31	100 (100)	4038
32	100 (100)	8436
35	65 (1)	-
40	36 (1)	-
41	100 (10)	343
42	9 (1)	-
43	98 (10)	354
44	29 (1)	-
45	18 (1)	-
46	10 (1)	-
48	85 (1)	468
49	9 (1)	-
50	2 (1)	-
51	100 (10)	778
52	26 (1)	-
53	99 (100)	202
54	12 (1)	-
55	13 (1)	-
56	32 (1)	-
57	5 (1)	-
58	97 (10)	484
59	54 (1)	-
60	100 (100)	296
65	98 (100)	1823
66	97 (100)	1044
67	100 (100)	254

102	100 (100)	503
103	14 (1)	-
104	99 (100)	394
105	100 (10)	387
106	100 (10)	237
107	99 (10)	304
108	18 (1)	-
109	45 (1)	-
110	99 (10)	314
111	76 (100)	41000
112	(-)2 (1)	-
114	98 (100)	84
115	71 (100)	51313
116	100 (10)	154
117	100 (100)	158
119	100 (10)	572
120	100 (100)	488
121	53 (100)	10565
122	15 (1)	-
123	99 (100)	256
124	99 (100)	285
125	6 (1)	-
126	79 (10)	4906
127	100 (100)	487
128	25 (1)	-
129	100 (100)	380
130	100 (100)	336
132	56 (10)	6215
133	97 (10)	315
134	100 (100)	2770
135	100 (100)	207
136	99 (100)	222

172	48 (1)	-
173	28 (1)	-
174	99 (10)	730
175	100 (100)	562
176	12 (1)	-
177	4 (1)	-
178	14 (1)	-
179	47 (10)	8871
180	95 (10)	2872
181	100 (10)	2240
182	83 (10)	4668
183	94 (10)	542
184	90 (10)	420
185	26 (1)	-
186	14 (1)	-
187	86 (1)	362
188	87 (10)	485
189	24 (1)	-
190	3 (1)	-
191	99 (1)	116
192	10 (1)	-
193	8 (1)	-
194	23 (1)	-
195	22 (1)	-
196	11 (1)	-
197	1 (1)	-
198	4 (1)	-
199	30 (1)	-
200	26 (1)	-
201	100 (10)	364
202	6 (1)	-
203	1 (1)	-

236	100 (10)	180
237	100 (100)	368
238	3 (1)	-
239	55 (10)	-
240	84 (10)	507
241	10 (1)	-
242	3 (1)	-
243	99 (10)	390
244	94 (10)	523
245	100 (100)	279
246	47 (1)	-
247	97 (10)	375
248	100 (10)	143
249	100 (10)	182
250	100 (100)	173
251	50 (1)	-
252	36 (1)	-
253	94 (10)	447
254	9 (1)	-
255	12 (1)	-
256	100 (10)	250
257	100 (10)	387
258	16 (1)	-
259	5 (1)	-
260	96 (10)	369
261	37 (1)	-
262	100 (10)	419
263	100 (10)	2932
264	100 (10)	42
265	90 (10)	3808

299		269
300		79
301		232
302		358
303		487
304		266
305		170
306		265
307		79
308		309
309		32
310		335
311		323
312		298
313		66
314		246
315		320
316		41
317		186
318		258
319		219
320		43
321		185
322		327
323		238
324		89
325		172
326		166
327		82
328		75

359		261
360		329

CD3 and CD28 Activation of Peripheral Blood T Cells and Determination of Secreted IL-2 Levels (C28 HU Assay)

Human peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hypaque seperation. PBMCs were stimulated with a combination of immobilized anti-CD3 and soluble anti CD28 mAbs as described in Faltynek, et al. *J. Enzyme Inhibition* **1995**, *9*, 111-122, hereby incorporated by reference. Following a 24 hour incubation, cell supernatants were harvested and IL-2 levels were determined. 100 µl of 5 µg/ml monoclonal murine anti-human IL-2 antibody (Biosource International) in D-PBS was added to 96 well Maxisorb plates (Nunc) and incubated at 4 °C overnight. Plates were washed 4 times with D-PBS containing 0.05% Tween 20 (wash buffer) and blocked with D-PBS containing 1% BSA and 10 mM NaN_3 (Diluent/Blocking buffer) for 1-3 hours at room temperature or overnight at 4 °C. Plates were washed and recombinant human IL-2 diluted (at 10,000, 5,000, 2,500, 1,250, 625, 312.5, 156.25, 78, 39, 20 pg/ml) in diluent/blocking buffer containing a matched percentage of complete RPMI 1640 medium as the unknown samples. Tissue culture supernatant at various dilutions were added in triplicate at 100 µl/well. Plates were incubated for 2 hours at room temperature and washed 4 times with wash buffer. 100 µl of rabbit anti-human IL-2 (10 µg/ml, Genzyme) was added and incubated for 1 hour at room temperature. The incubation was followed by 4 washes and subsequent addition of 100 µl of 1:2000 dilution of alkaline phosphatase-conjugated goat anti-rabbit $F(ab')_2$ (Biosource International). After 1 hour the plates were washed 4 times and 100 µl of pNPP (Southern Biotech or Sigma) at 1 mg/ml in buffer was added. Color development was allowed to proceed at room temperature for 20 minutes before addition of 50 µl of 2 N NaOH. Absorbance at 405 nm was determined using a plate reader (Molecular Devices). IL-2 concentrations were calcualted using SoftMax (Molecular Devices) based on the IL-2 standard solutions.

Table 2

Inhibition of IL-2 Secretion by Representative Compounds in the C28 Assay

serum, 100 U/mL penicillin and 100 µg/mL streptomycin. Cultures were then centrifuged, to pellet the cells, and cells resuspended in fresh medium to the same density. 0.2 mL samples of cells were incubated in 96-well plates with 8 µL of various concentrations of compound freshly diluted with the above medium from 100 mM solvent stocks (ethanol or DMSO). Immediately after addition of compound, cells were stimulated by addition of 2 ng/mL phorbol 12-myristate 13-acetate (1 µL of freshly prepared solution of stock (in DMSO) diluted with the above medium added to cells) and 750 µg/mL anti-CD3 (pre-coated at 4 °C overnight). Cell cultures were incubated at 37 °C for 32 hours, then cells pelleted by centrifugation and the supernatants harvested for ELISA. IL-4 and IL-5 ELISA's were performed according to standard procedures. Inhibition was calculated relative to cytokine levels produced from control stimulated cells not treated with compound.

Table 3

Inhibition of IL-4 and IL-5 Secretion in Human T Cells by Representative Compounds and Comparison with FK-506

Example Number	IL-4 Inhibition IC_{50} (nM)	IL-5 Inhibition IC_{50} (nM)
FK-506	0.7	0.5
24	150	150
250	50	80
266	110	150
209	5	38
6	8	50
264	4.8	22

As shown in Tables 1, 2 and 3, the compounds are useful for inhibiting cytokine (IL-2, IL-4 and IL-5) production and cellular proliferation in stimulated human T cell lines or human peripheral blood mononuclear cells and therefore have utility in the treatment of diseases that are prevented by or ameliorated with cytokine inhibitors.

The compounds of the invention, including but not limited to those specified in the examples, possess immunomodulatory activity in mammals, especially humans. As immunosuppressants, the compounds of the present invention are useful for the treatment and

photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases such as arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis; collagen diseases such as scleroderma, Wegener's granuloma and Sjogren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease such as lesions of gingiva, periodontium, alveolar bone and substantia ossea dentis; nephrotic syndrome such as glomerulonephritis; male pattern aleopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth; muscular dystrophy; Pyoderma and Sezary's syndrome; Addison's disease; active oxygen-mediated diseases, as for example organ injury such as ischemia-reperfusion injury of organs (such as heart, liver, kidney and digestive tract) which occurs upon preservation, transplantation or ischemic disease (for example, thrombosis and cardiac infarction); intestinal diseases such as endotoxin-shock, pseudomembranous colitis and colitis caused by drug or radiation; renal diseases such as ischemic acute renal insufficiency and chronic renal insufficiency; pulmonary diseases such as toxinosis caused by lung-oxygen or drug (for example, paracort and bleomycins), lung cancer and pulmonary emphysema; ocular diseases such as cataracta, siderosis, retinitis, pigmentosa, senile macular degeneration, vitreal scarring and corneal alkali burn; dermatitis such as erythema multiforme and others such as sinusitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenesis, metastasis of carcinoma and hypobaropathy; diseases caused by histamine or leukotriene-C_4 release; Behcet's disease such as intestinal-, vasculo- or neuro-Behcet's disease, and also Behcet's which affects the oral cavity, skin, eye, vulva, articulation, epididymis, lung, kidney and so on. Furthermore, the compounds of the invention are useful for the treatment and prevention of hepatic disease such as immunogenic diseases (for example, chronic autoimmune liver diseases such as autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxin, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis, cirrhosis (such as alcoholic cirrhosis) and hepatic failure such as fulminant hepatic failure, late-onset hepatic failure and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases), and moreover are useful for various diseases because of their useful activity such as augmention of chemotherapeutic effect, cytomegalovirus infection, particularly HCMV infection, anti-inflammatory activity, sclerosing and fibrotic diseases such as nephrosis, scleroderma, pulmonary fibrosis, arteriosclerosis, congestive heart failure, ventricular hypertrophy, post-surgical adhesions and scarring, stroke, myocardial infarction and injury associated with ischemia and reperfusion, and the like.

absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants such as glycerol; d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents such as paraffin; f) absorption accelerators such as quaternary ammonium compounds; g) wetting agents such as cetyl alcohol and glycerol monostearate; h) absorbents such as kaolin and bentonite clay and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols, and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally or in delayed fashion. Examples of embedding compositions that can be used include polymeric substances and waxes.

ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories that can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax that are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

The compounds of this invention can be prepared by a variety of synthetic routes. Representative procedures are shown in Schemes 1-12 wherein R_1, R_2, R_3, R_4, R_5, L_3, Q, B and E are defined above unless otherwise indicated.

Abbreviations

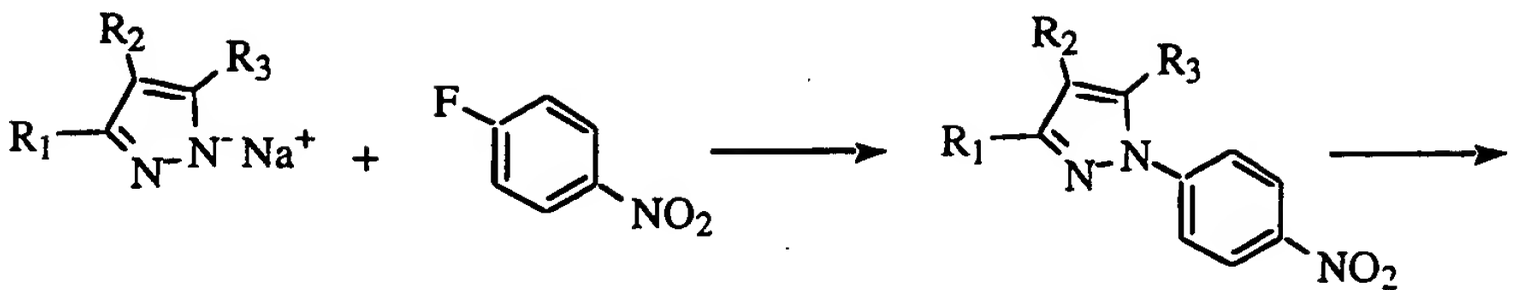
Abbreviations that have been used in the descriptions of the schemes and the examples that follow are: THF for tetrahydrofuran; DMF for N,N-dimethylformamide; DMSO for dimethylsulfoxide; Boc for tert-butylcarbonyloxy; DCC for dicyclohexylcarbodiimide; EDC for 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HBTU for O-benzotriazol-yl-N,N,N'N'-tetramethyluronium hexafluorophosphate; and DMAP for 4-dimethylaminopyridine. Starting materials, reagents and solvents were purchased from Aldrich Chemical Company (Milwaukee, WI), Maybridge Chemical Company (Tintagel, Cornwall, U.K.), Lancaster (Windham, NH), Sigma (St. Louis, MO), ACROS, and Chess (Mannheim, Germany).

Description of Intermediates in the Schemes

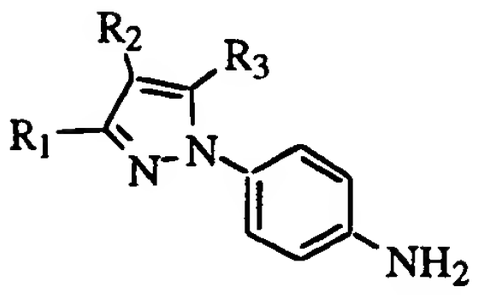
Compounds of Formula **I** are designated by the small-case numbers (i), (ii), (iii), (iv), etc. The small-case letters ("-a," "-b," and "-c") that follow the small-case numbers indicate the disposition of the substituent **E** on ring **Q** relative to the position of the pyrazole or triazole ring as defined in the schemes 1-12. Intermediates in the syntheses of compounds of Formula **I** are further designated by a capital letter (A, B, C, etc).

palladium on carbon. An alternative method was reduction with tin(II) chloride in the presence of acid, preferably hydrochloric acid, at elevated temperature. A more preferred method of reduction was with iron powder with ammonium chloride in ethanol/water.

Scheme 3



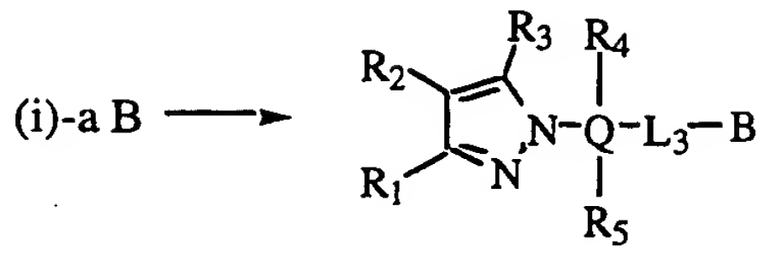
Example (xxii)-a A



Example (xxii)-a B

As shown in Scheme 3, an alternative route to aniline precursors was direct displacement of a leaving group, preferably fluoride, from 4-fluoronitrobenzene by the sodium salt of a preformed, substituted pyrazole ring followed by conversion of the nitro intermediate (xxii)-a A to aniline precursor (xxii)-a B with reducing agents such as those described in Scheme 1.

Scheme 5



Formula **I**

Example (ii)-a $-L_3-$ is $-NHC(O)NH-$

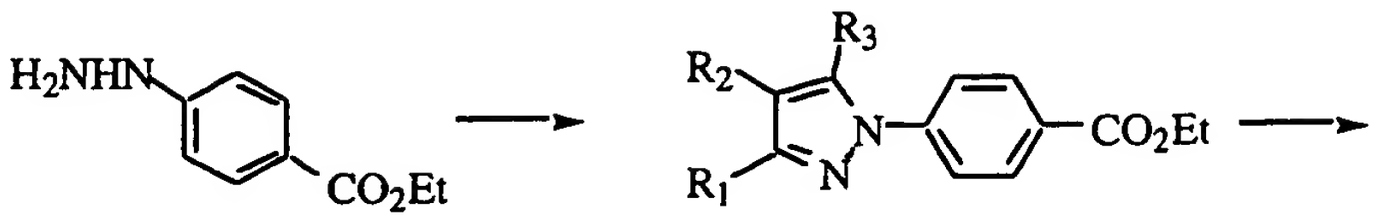
Example (iii)-a $-L_3-$ is $-NHSO_2-$

Example (vi)-a $-L_3-$ is $-NH(CH_2)_m-$

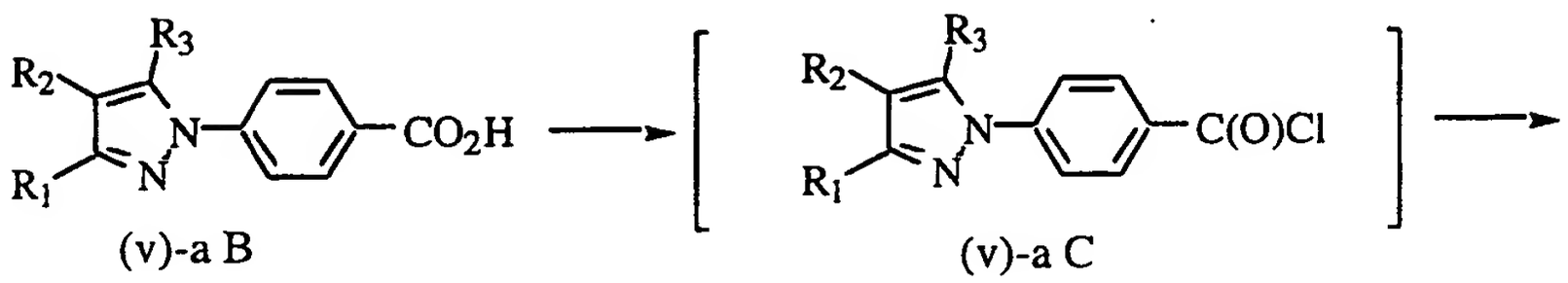
As shown in Scheme 5, conversion of Example (i)-a B to compounds of Formula **I**, as exemplified by examples (ii)-a, (iii)-a, and (vi)-a, was achieved by treatment of Example (i)-a B with isocyanates, sulfonyl chlorides, or aldehydes in the presence of appropriate reducing agents, respectively.

(xii)-a, (xiii)-a, (xiv)-a, (xv)-a, (xvi)-a, and (xvii)-a by the coupling conditions described in Scheme 4.

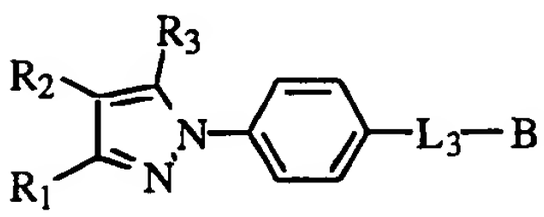
Scheme 8



(v)-a A



(v)-a B (v)-a C



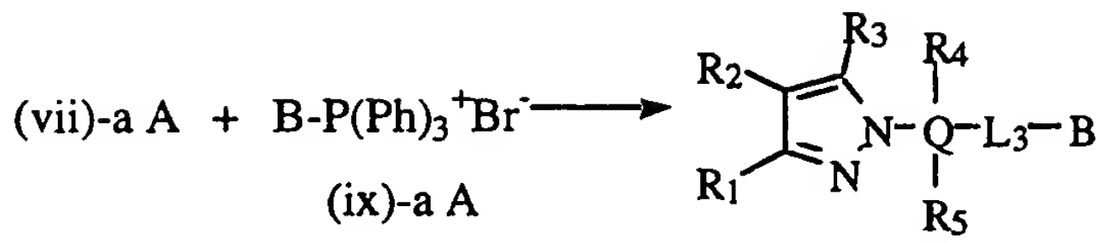
Formula I

$-L_3-$ is -C(O)NH-

(v)-a

As shown in Scheme 8, compounds of Formula I derived from intermediates other than anilines were prepared from intermediate ester Example (v)-a A. Construction of the pyrazole ring from ethyl 4-hydrazinobenzoate according to Example (i)-a (Method 1) provided Example (v)-a A which was then hydrolyzed to carboxylic acid (v)-a B with base, preferably sodium hydroxide. Example (v)-a B was then elaborated to compounds of Formula I by conversion to the acid chloride (v)-a C with reagents such as thionyl chloride followed by treatment with amines in the presence of a base such as pyridine or triethylamine.

Scheme 10



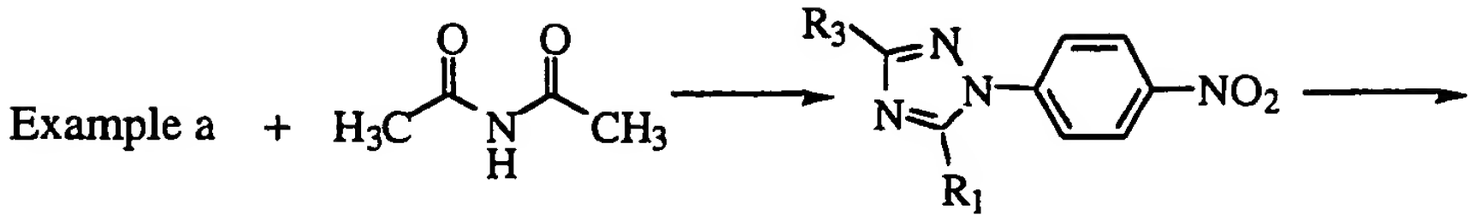
Formula I

(ix)-a

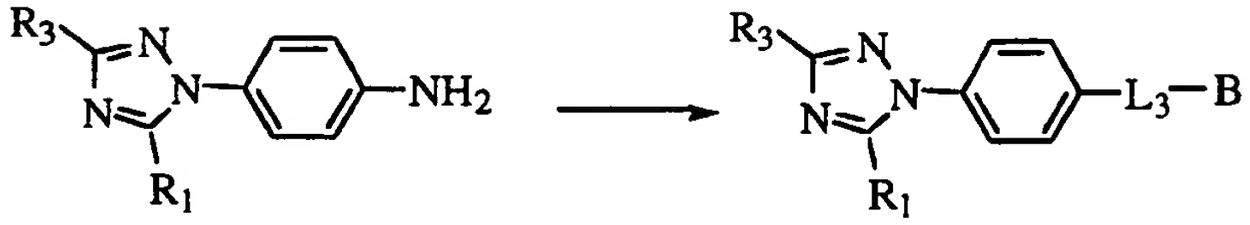
L_3 is Z and E alkenylene

As shown in Scheme 10, treatment of Example (vii)-a A with ylides such as Example (ix)-a A also provided compounds of Formula **I** (exemplified by (ix)-a).

Scheme 12



(xxv)-a A



(xxv)-a B

Formula **I**

L_3 is -NHC(O)-

(xxv)-a

As shown in Scheme 12, construction of the substituted triazole rings of the compounds of Formula **I** was achieved by treatment of Example a (4-nitrophenylhydrazine) with diacetamide in the presence of acid, preferably sulfuric acid, to provide nitro intermediate (xxv)-a A. Example (xxv)-a A was converted to aniline intermediate (xxv)-a B with reducing agents such as those described in Scheme 1. Example (xxv)-a B was then converted to compounds of Formula **I** by the coupling chemistry described in scheme 4.

Example (i)-a, (i)-b, and (i)-c

Compounds of Formula **I** where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-, 1,3-, and 1,2-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-N(R_6)C(W)-$ where W is O and R_6 is H

Example (i)-a A, (i)-b A, and (i)-c A (Method 1)

A solution of a, b, or c (1 equivalent), 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (1.2 equivalents), and p-toluenesulfonic acid (1 mmol) in toluene was refluxed for 18 hours in a Dean-Stark apparatus, diluted with ethyl acetate, washed sequentially with 1M HCl and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by

Compounds of Formula I (Method 5)

A solution of (i)-a B (1 equivalent), B-C(O)Cl (2 equivalents), and polyvinylpyridine in dichloromethane in a capped test tube was shaken overnight, treated with a primary benzyl amine resin, preferably Aminomethyl Resin·HCl (Midwest Bio-Tech, Fishers, IN) shaken for an additional 2 hours, eluted through a silica gel plug with acetone, and concentrated. The residue was purified by flash chromatography on silica gel to provide the desired compounds.

Example (i)-a

Compounds of Formula I (Method 6)

A solution of (i)-a B (1 equivalent), B-C(O)Cl (1-1.5 equivalents), and base (preferably pyridine or triethylamine, 1-10 equivalents) in an appropriate solvent, preferably dichloromethane or THF, was shaken overnight in a capped test tube, diluted with ethyl acetate, washed with saturated $NaHCO_3$ and 1M HCl, and concentrated. The residue was purified by flash chromatography on silica gel to provide the desired compounds.

Example (i)-a

Compounds of Formula I (Method 7)

Example (i)-a B (1 equivalent), the appropriate carboxylic acid (B-CO_2H, 1-2 equivalents), and EDC (1-1.5 equivalents), and DMAP (catalytic to 1 equivalent) in dichloromethane was shaken in a capped test tube for 18 hours at a temperatures between 25 and 60 °C, extracted with 1N hydrochloric acid and water, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel to provide the desired compounds.

Example (i)-b

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,3-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is -N(R_6)C(W)-; W is O and R_6 is H

Example (i)-b B was processed as in Example (i)-a B (Method 5, 6, or 7) to provide the desired compounds.

Example (i)-c

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-C(W)N(R_6)-$; W is O; and R_6 is H

Example (v)-a A

A solution of ethyl 4-hydrazinobenzoate (1 equivalent) and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (1.1 equivalents) in 4M HCl/ethanol were heated to reflux for 18 hours and concentrated. The residue was dissolved in dichloromethane and eluted through a silica gel plug with dichloromethane to provide the desired compound.
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.17 (d, 2H), 7.91 (s, 1H), 7.8 (d, 2H), 4.38 (q, 2H), 1.35 (t, 3H).

Example (v)-a B

A solution of Example (v)-a A (1 equivalent) and NaOH (5 equivalents) in ethanol was heated to reflux for 2 hours, concentrated, redissolved in water, acidified with 1N HCl to pH~4, and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated to provide the desired compound.
^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.4 (bs, 1H), 8.15 (d, 2H), 7.88 (s, 1H), 7.77 (d, 2H).

Example (v)-a C

Compounds of Formula I

A solution of Example (v)-a B (1 equivalent) in thionyl chloride (22 equivalents) was heated to reflux for 3 hours and concentrated.

Example (v)-a (Method 11)

Compounds of Formula I

Example (v)-a C in dichloromethane was treated with amine (H_2N-B, 1 equivalent) in the presence of pyridine (4 equivalents), and purified by flash chromatography on silica gel to provide the desired compounds.

Example (vi)-a (Method 12)

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-NR_6(alkylene)_m-$, R_6 is hydrogen, and m is 1

A mixture of Example (vii)-a A (1 equivalent) and the appropriate amine (B-NH_2, 1.1 equivalent) in dichloroethane (3 mL) at room temperature was treated sequentially with acetic acid (1.0 equivalent) and sodium triacetoxyborohydride (1.5 equivalents), shaken for 4 hours at room temperature, washed with brine, eluted through a $MgSO_4$/silica gel plug with 10% acetone/hexanes, concentrated, and purified on silica gel with 10% acetone/hexanes to provide a mixture of the desired compounds.

Example (ix)-a

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is alkenylene

Example (ix)-a A

A solution of halide (B-Br where B is C_1-C_6 alkyl substituted with substituted aryl, 1 equivalent) and triphenylphosphine (1.2 equivalents) in toluene was heated to reflux for 2 hours, filtered, washed with toluene and dried under vacuum to provide the desired compounds.

Example (ix)-a Compounds of Formula I (Method 14)

A solution of sodium methoxide (prepared by the addition of sodium metal (1.06 equivalents) in methanol) was treated with Example (ix)-a A (1.0 equivalents) stirred at room temperature for 30 minutes, treated with Example (vii)-a A (1 equivalent), heated to reflux for 2 hours, cooled, treated with brine and extracted with diethyl ether. The extract was dried (Na_2SO_4), and concentrated. The residue was purified by HPLC eluting with acetone/hexanes to provide the desired compounds as a mixtures of Z (major) and E (minor) isomers.

Example (x)-a

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 is hydrogen; R_5 is alkoxycarbonyl; L_3 is -$N(R_6)C(W)$-; W is O; R_6 is hydrogen

Example (x)-a A

2-Fluoro-5-nitrobenzoic acid in 3:1 methanol/THF at 0 °C was treated dropwise with (trimethylsilyl)diazomethane to a yellow endpoint, stirred for 36 hours at room temperature,

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.78 (s, 1H), 7.4 (d, 1H), 7.03 (d, 1H), 6.84 (dd, 1H), 6.25 (s, 2H).

Example (xi)-aCompounds of Formula I

Example (xi)-a B was processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

Example (xii)-a

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 is hydrogen; R_5 is CF_3; L_3 is -N(R_6)C(W)-; W is O; R_6 is hydrogen

Example (xii)-a A

4-Fluoro-2-trifluoromethylnitrobenzene was processed as in Example (x)-a B to provide the desired compound.

Example (xii)-a B

Example (xii)-a A was processed by Method 3 to provide the desired compound.
^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75 (s, 1H), 7.6 (d, 1H), 7.46 (dd, 1H), 6.95 (d, 1H), 6.22 (s, 2H).

Example (xii)-aCompounds of Formula I

Example (xii)-a B was processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

Example (xiii)-a

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 is hydrogen; R_5 is halo; L_3 is -N(R_6)C(W)-; W is O; R_6 is hydrogen

Example (xiii)-a A

4-Bromo-3-chloronitrobenzene was processed as in Example (x)-a B to provide the desired compound.

4-Fluoro-2-methoxynitrobenzene was processed as in Example (x)-a B and purified by flash chromatography on silica gel with 1:70:30 ethyl acetate/pentane/dichloromethane to provide the desired compound.

Example (xv)-a B

Example (xv)-a A was processed by Method 3 to provide the desired compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.73 (s, 1H), 6.99 (d, 1H), 6.85 (dd, 1H), 6.7 (d, 1H, 3.88 (s, 3H).

Example (xv)-aCompounds of Formula I

Example (xv)-a B was processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

Example (xvi)-a

Compounds of Formula I where

R_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 is hydrogen; R_5 is halo; L_3 is -N(R_6)C(W)-; W is O; R_6 is hydrogen

and

Example (xvii)-aR_1 and R_3 are CF_3; R_2 is H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 is hydrogen; R_5 is substituted heterocycle; L_3 is -N(R_6)C(W)-; W is O; R_6 is hydrogen

Example (xvi)-a A and Example (xvii)-a A

2,4-Difluoronitrobenzene was processed as in Example (x)-a B to provide a mixture of the desired compounds.

Example (xvi)-a B and Example (xvii)-a B

Examples (xvi)-a A and Example (xvii)-a A were processed by Method 3 to provide a mixture the desired compounds.
^{1}H NMR (DMSO-d_6, 300 MHz) (mixture of (xvi)-a B and (xvii)-a B) (xvi)-a B: δ 7.74 (s, 1H), 7.19 (m, 2H), 6.84 (dd, 1H), 5.18 (s, 2H) and (xvii)-a B: δ 7.74 (s, 1H), 7.72 (s, 1H), 7.52 (d, 1H), 7.48 (dd, 1H), 6.94 (d, 1H), 5.95 (s, 2H).

Example (xvi)-a and Example (xvii)-a

Compounds of Formula I

(xviii)-a

Compounds of Formula I

and

(xix)-a

Compounds of Formula I

Example (xviii)-a B and Example (xix)-a B were each processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

(xx)-a

Compounds of Formula I where

R_1 is CH_3; R_2 and R_3 are H; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-N(R_6)C(W)-$; W is O; and R_6 is H

and

(xxi)-a

R_1 and R_2 are H; R_3 is CH_3; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-N(R_6)C(W)-$; W is O; and R_6 is H

Example (xx)-a A and (xxi)-a A

4-Nitrophenylhydrazine and acetylacetaldehyde dimethylacetal were processed as in Example (xviii)-a A/Example (xix)-a A and purified by flash chromatography on silica gel with 0.5:5:5 ethyl acetate/dichloromethane/pentane to provide the desired compounds. (xx)-a A: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.32 (d, 2H), 7.93 (d, 1H), 7.84 (d, 2H), 6.36 (d, 1H), 2.4 (s, 3H) and (xxi)-a A: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (d, 2H), 7.73 (d, 2H), 7.64 (d, 1H), 6.28 (d, 1H), 2.48 (s, 3H).

Example (xx)-a B

Example (xx)-a A was processed by Method 3 to provide the desired compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, 1H), 7.05 (d, 2H), 6.75 (d, 2H), 6.20 (d, 1H), 2.38 (s, 3H).

Example (xxi)-a B

Example (xxi)-a A was processed by Method 3 to provide the desired compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.42 (s, 1H), 7.08 (dd, 2H), 6.62 (dd, 2H), 6.17 (s, 1H), 5.3 (br s , 2H), 2.22 (s, 3H).

Compounds of Formula I where
R_1 is CF_3; R_2 is H; R_3 is hydroxyl; Z is carbon; Q is 1,4-disubstituted phenyl; R_4 and R_5 are hydrogen; L_3 is $-N(R_6)C(W)-$; W is O; and R_6 is H

Example (xxiii)-a A

A solution of ethyl 4,4,4-trifluoroacetoacetate (10 g, 54 mmol) and 4-nitrophenylhydrazine (8.3 g, 54 mmol) in ethanol (200 mL) was treated with concentrated sulfuric acid (0.5 ml), refluxed for 25 minutes, and concentrated. The residue was dissolved in ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated to provide the desired compound.
^{1}HNMR ($CDCl_3$, 300 MHz) δ 9.8 (s, 1H), 8.21 (d, 2H), 7.23 (d, 2H), 4.27 (q, 2H), 3.56 (s, 2H), 1.24 (t, 3H).

Example (xxiii)-a B

A solution of Example (xxiii)-a A (7.7 g. 24.2 mmol) in 2:1 ethanol:dichloromethane (300 mL) was treated with anhydrous K_2CO_3 (6.7g, 48.4 mmol), stirred at room temperature for 18 hours, and concentrated. The residue was neutralized with dilute HCl, extracted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated. The residue was flash chromatographed on silica gel with 5% methanol/dichloromethane to provide the desired compound.
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.38 (d, 2H), 8.15 (d, 2H), 5.9 (s, 1H).

Example (xxiii)-a C

Example (xxiii)-a B was processed by Method 3 to provide the desired compound.
^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.24 (d, 2H), 6.62 (d, 2H), 5.85 (s, 1H), 5.4 (m, 2H).

Example (xxiii)-a
Compounds of Formula I

Example (xxiii)-a C was processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

Example (xxiv)-a
Compounds of Formula I where

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.18 (d, 2H), 6.7 (d, 1H), 5.45 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H).

Example (xxv)-a

Compounds of Formula I

Example (xxv)-a B was processed by Method 5, 6, or 7 to provide the desired compounds of Formula I.

Example 1

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopropanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 204-205 °C;

MS (DCI/NH_3) m/e 381 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.52 (s, 1H), 7.79 (d, 2H), 7.78 (s, 1H), 7.53 (d, 2H), 1.81 (m, 1H), 0.85 (d, 4H).

Example 2

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2,3,3-tetramethylcyclopropanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 171-172 °C;

MS (DCI/NH_3) m/e 437 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.78 (s, 1H), 7.77 (d, 2H), 7.5 (d, 2H), 1.33 (s, 1H), 1.26 (s, 6H),1.2 (s, 6H).

Example 3

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2-dichloro-1-methylcyclopropanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 143-145 °C;

MS (ESI-) m/e 445 $(M-H)^-$;

mp 172-173 °C;
MS (DCI/NH_3) m/e 395 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.8 (s, 1H), 7.78 (d, 2H), 7.54 (d, 2H), 1.57 (m, 1H), 1.27 (m, 1H), 1.12 (d, 3H), 1.05 (m, 1H), 0.7 (m, 1H);

Example 8

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-(3,5-dichlorophenoxy)-2-furancarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 152-153 °C;
MS (DCI/NH_3) m/e 551 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.45 (s, 1H), 7.95 (d, 2H), 7.82 (s, 1H), 7.6 (d, 2H), 7.55 (t, 1H), 7.47 (d, 1H), 7.4 (d, 2H), 6.15 (d, 1H).

Example 9

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-2-cyclohexene-1-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 108-110 °C;
MS (ESI-) m/e 416 $(M-H)^-$;
^1H NMR ($CDCl_3$, 300 MHz) δ 7.70 (d, 3H), 7.43 (d, 2H), 7.05 (s, 1H), 5.90-5.65 (m, 2H), 2.63-2.45 (m, 1H), 2.20-1.85 (m, 4H), 1.60-1.60 (m, 1H), 1.25 (s, 3H).

Example10

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-cyclopentene-1-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 174-175 °C;
MS (DCI/NH_3) m/e 407 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 9.95 (s, 1H), 7.90 (d, 2H), 7.79 (s, 1H), 7.55 (d, 2H), 6.78 (m, 1H), 2.64-2.46 (m, 4H), 1.93 (m, 2H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.25 (s, 1H), 8.43 (s, 1H), 7.95 (d, 2H), 7.83 (s, 2H), 7.6 (d, 2H), 7.03 (s, 1H).

Example 15

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methyl-3-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 194-195 °C;

MS (DCI/NH_3) m/e 476 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.95 (s, 1H), 8.04 (d, 1H), 7.95 (d, 2H), 7.85 (d, 1H), 7.82 (s, 1H), 7.64 (d, 2H,), 7.6 (t, 1H), 2.48 (s, 3H).

Example 16

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-cyanophenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 204-205 °C;

MS (DCI/NH_3) m/e 457 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.24 (s, 1H), 9.16 (s, 1H), 7.98 (t, 1H), 7.79 (s, 1H), 7.73-7.65 (m, 3H), 7.54 (d, 2H), 7.43 (dd, 2H).

Example 17

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-hydroxycyclopropanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 198-200 °C;

MS (DCI/NH_3) m/e 397 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1H), 7.98 (d, 2H), 7.81 (s, 1H), 7.54 (d, 2H), 6.64 (s, 1H), 1.19 (m, 1H), 1.1 (t, 2H), 1.0 (m, 1H).

Example 18

N-[4[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cycloheptanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

2-Benzoyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 204-205 °C;
MS (DCI/NH_3) m/e 521 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.9 (d, 3H), 7.8 (s, 1H), 7.69-7.57 (m, 2H), 7.53 (d, 2H), 7.42 (d, 2H), 7.35-7.22 (m, 4H).

Example 23

3a(S)-(3aα,4β,6aα)-N-[4–[3,5–bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]hexahydro-2-oxo-1H-thieno[3,4-d]imidazole-4-pentanamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 185-186 °C;
MS (ESI) m/e 522 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.22 (s, 1H), 7.8 (d, 2H), 7.79 (s, 1H), 7.53 (d, 2H), 6.41 (s, 1H), 6.33 (s, 1H), 4.31 (m, 1H), 4.15 (m, 1H), 3.14 (m, 1H), 2.83 (dd, 1H), 2.59 (d, 1H), 2.37 (t, 2H), 1.35-1.7 (m, 6H).

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N-4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-chlorophenyl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 183-185 °C;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.69 (s, 1H), 8.23-8.10 (m, 1H), 8.07-8.03 (m, 4H), 7.87 (s, 1H), 7.86-7.72 (m, 4H);
MS (DCI/NH_3) m/e 451$(M+NH_4)^+$.

Example 25

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-iodobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 192-193 °C;
MS (DCI/NH_3) m/e 543 $(M+NH_4)^+$;

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 177-178 °C;

MS (DCI/NH_3) m/e 421 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.91 (d, 2H), 7.88 (s, 1H), 7.63 (d, 2H), 5.80 (s, 2H), 2.75 (m, 1H), 2.35-2.20 (m, 2H), 2.22-1.97 (m, 2H), 2.05-1.99 (m, 1H), 1.77-1.62 (m, 1H).

Example 30

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-fluorophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 194-195 °C;

MS (DCI/NH_3) m/e 417 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.58 (s, 1H), 8.15 (d, 2H), 7.9 (s, 1H), 7.81 (d, 2H), 7.8 (d, 2H), 7.23 (t, 2H).

Example 31

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-nitrophenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 203-204 °C;

MS (DCI/NH_3) m/e 477 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.42 (s, 1H), 9.38 (s, 1H), 8.58 (t, 1H), 7.84 (d, 1H), 7.80 (s, 1H), 7.77 (d, 1H), 7.70 (d, 2H), 7.60 (d, 1H), 7.53 (d, 2H).

Example 32

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-fluorophenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 201-202 °C;

MS (DCI/NH_3) m/e 450 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.50 (s, 1H), 9.21 (s, 1H), 8.19 (s, 1H), 8.07 (d, 2H), 7.96-7.83 (m, 4H), 7.55 (t, 2H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.07 (s, 1H), 8.81 (s, 1H), 7.80 (s, 1H), 7.66 (d, 2H), 7.52 (d, 2H), 7.49 (d, 2H), 7.30 (t, 2H), 7.00 (t, 1H).

Example 38

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-chloro-2-methylphenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 193-196 °C;

MS (DCI/NH_3) m/e 480 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.39 (s, 1H), 8.28 (s, 1H), 7.78 (s, 1H), 7.72 (t, 1H), 7.67 (d, 2H), 7.52 (d, 2H), 7.22- 7.15 (m, 2H), 2.31 (s, 3H).

Example 39

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-[4-(butyloxyphenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 193-196 °C;

MS (DCI/NH_3) m/e 504 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.10 (s, 1H), 8.71 (s, 1H), 7.91 (s, 1H), 7.77 (d, 2H), 7.63 (d, 2H), 7.49 (d, 2H), 7.01 (d, 2H), 4.06 (t, 2H), 1.83-1.78 (m, 2H), 1.57-1.53 (m, 2H), 1.06 (t, 3H).

Example 40

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-methyl-3-nitrophenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 235-236 °C;

MS (DCI/NH_3) m/e 491 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.46 (s, 1H), 8.46 (s, 1H), 8.05 (dd, 1H), 7.79 (s, 1H), 7.68 (d, 2H), 7.60 (dd, 1H), 7.54 (d, 2H), 7.43 (t, 1H), 2.31 (s, 3H).

Example 41

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-chloro-4-nitrophenyl)urea

Example 45

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-bromo-2,6-dimethylphenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp >230 °C;

MS m/e (ESI-) m/e 519 $(M-H)^-$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.20 (s, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 7.65 (d, 2H), 7.48 (d, 2H), 7.33 (s, 1H), 2.22 (s, 6H).

Example 46

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(1H-pyrrol-1-yl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 249-252 °C;

MS (DCI/NH_3) 482 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.58 (br s, 1H), 8.04 (d, 2H), 8.01 (d, 2H), 7.81 (d, 2H), 7.80 (s, 1H), 7.61 (d, 2H), 7.56 (t, 2H), 6.37 (t, 2H).

Example 47

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-heptylurea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 129-130 °C;

MS (DCI/NH_3) m/e 454 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.58 (d, 2H), 7.45 (s, 1H), 7.40 (d, 2H), 3.18 (t, 2H), 2.60 (quintet, 4H), 1.40-1.25 (m, 6H), 0.90 (t, 3H).

Example 48

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-chloro-2-nitrophenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.

mp 225-227 °C;

MS (DCI/NH_3) m/e 511 $(M+NH_4)^+$;

mp 140-143 °C;
MS (DCI/NH_3) m/e 380 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 7.8 (s, 1H), 7.7 (d, 2H), 7.6 (d, 2H), 4.0 (s, 2H).

Example 53

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-cyclohexane-1-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 126-128 °C;
MS (DCI/NH_3) m/e 421 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.3 (br, s, 1H), 7.8 (s, 1H), 7.8 (d, 2H), 7.6 (d, 2H), 5.7 (s, 2H), 2.6 (m, 1H), 2.2 (m, 2H), 2.1 (m, 2H), 1.9 (m, 1H), 1.5 (m, 1H).

Example 54

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylcyclohexanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
MS (DCI/NH_3) m/e 437 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 12.0 (br, s, 1H), 7.8 (d, 2H), 7.8 (s, 1H), 7.5 (d, 2H), 2.4 (t, 1H), 1.9 (m, 4H), 1.4 (m, 4H), 1.3 (m, 1H), 0.9 (d, 3H).

Example 55

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methoxy-α-(trifluoromethyl)benzeneacetamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 127-129 °C;
MS (DCI/NH_3) m/e 529 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (m, 4H), 7.5 (m, 3H), 3.6 (s, 3H).

Example 56

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]heptanamide

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.97 (d, 2H), 7.83 (s, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 6.62 (d, 2H), 5.84 (s, 2H).

Example 60

4-Azido-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 182-184 °C;

MS (DCI/NH_3) m/e 458 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 8.1 (d, 2H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.3 (d, 2H).

Example 61

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-thiopheneacetamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 181-183 °C;

MS (DCI/NH_3) m/e 437 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 7.8 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.4 (dd, 1H), 7.0 (m, 2H), 3.9 (s, 2H).

Example 62

N-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-tricyclo[3.3.1.1^{3,7}]-decanecarboxmide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 213-214 °C;

MS (DCI/NH_3) m/e 475 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.4 (s, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.5 (d, 2H), 2.1 (s, 3H), 1.9 (s, 6H), 1.7 (s, 6H).

Example 63

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N^2-[(1,1-dimethylethoxy)carbonyl]-L-asparagine, phenylmethyl ester

Example 67

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 169-171 °C;

MS (DCI/NH_3) m/e 442 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.8 (s, 1H), 8.2 (d, 2H), 8.1 (d, 2H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H).

Example 68

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenylcyclopropanecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 176-178 °C;

MS (DCI/NH_3) m/e 457 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 7.8 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.3 (m, 2H), 7.2 (m, 3H), 2.4 (m, 1H), 2.1 (m, 1H), 1.6 (m, 1H), 1.4 (m, 1H).

Example 69

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-iodobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 196-198 °C;

MS (DCI/NH_3) m/e 543 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 8.0 (d, 2H), 7.9 (d, 2H), 7.8 (s, 1H), 7.7 (d, 2H), 7.6 (d, 2H).

Example 70

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloropropanamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 144-145 °C;

MS (DCI/NH_3) m/e 403 $(M+NH_4)^+$;

mp 153-155 °C;
MS (DCI/NH_3) m/e 517 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.4 (s, 1H), 8.0 (m, 4H), 7.8 (s, 1H), 7.6 (d, 2H), 7.1 (d, 2H), 4.1 (t, 2H), 1.8-1.7 (m, 2H), 1.5-1.4 (m, 2H), 1.4-1.3 (m, 4H), 0.9-0.8 (m, 3H).

Example 75

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methylbenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 137-139 °C;
MS (DCI/NH_3) m/e 431 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.5 (s, 1H), 8.0 (d, 2H), 7.9 (s, 1H), 7.8 (m, 2H), 7.6 (d, 2H), 7.4 (dd, 2H), 2.4 (s, 3H).

Example 76

2-(Acetyloxy)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 159-161 °C;
MS (DCI/NH_3) m/e 475 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.7 (s, 1H), 8.0 (d, 2H), 7.9 (s, 1H), 7.8 (dd, 1H), 7.6 (d, 2H), 7.4 (m, 1H), 7.3 (dd, 1H), 2.2 (s, 3H).

Example 77

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-bromo-2-methylphenyl)urea

Example (i)-a B was processed as in Example (ii)-a (Method 8) to provide the title compound.
mp 230-231 °C;
MS (DCI/NH_3) m/e 474 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 9.26 (s, 1H), 9.21 (s, 1H), 7.93 (d, 2H), 7.81 (s, 1H), 7.68 (d, 2H), 7.61 (d, 2H), 7.54 (dd, 1H), 2.55 (S, 3H).

Example 78

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4,6-trimethylbenzamide

Example (i)-a B was processed as in Example (vi)-a (Method 12) to provide the title compound.
mp 240 °C;
MS (DCI/NH_3) m/e 420 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.70 (s, 1H), 7.54-7.47 (m, 1H), 7.45-7.41 (m, 1H), 7.38-7.32 (m, 2H), 7.25 (d, 2H), 6.90 (t, 1H), 6.67 (d, 2H), 4.40 (d, 2H).

Example 83

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-5-nitro-1H-pyrazole-4-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 214-216 °C;
MS (DCI/NH_3) m/e 466 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.83 (s, 1H), 8.03 (s, 1H), 7.89 (d, 2H), 7.87 (s, 1H), 7.63 (d, 2H).

Example 84

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluorobenzenemethanamine

Example (i)-a B was processed as in Example (vi)-a (Method 12) to provide the title compound.
mp 92-94 °C;
MS (DCI/NH_3) m/e 404 $(M+H)^+$ and 421 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.68 (s, 1H), 7.45-7.38 (m, 2H), 7.24-7.13 (m, 4H), 6.87 (t, 1H), 6.68 (d, 2H), 4.33 (d, 2H).

Example 85

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-bromobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 205-207 °C;
MS (DCI/NH_3) m/e 495 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 8.0 (d, 2H), 7.9 (d, 2H), 7.8 (s, 1H), 7.8 (d, 2H), 7.6 (d, 2H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.6 (s, 1H), 8.1 (m, 2H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.4 (m, 2H).

Example 91

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chlorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 155-157 °C;

MS (DCI/NH_3) m/e 451 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.9 (s, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.6-7.4 (m, 4H).

Example 92

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 177-178 °C;

MS (DCI/NH_3) m/e 417 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.0-7.9 (m, 4H), 7.6 (m, 3H), 7.5 (m, 3H).

Example 93

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 185-188 °C;

MS (DCI/NH_3) m/e 462 $(M+NH_4)^+$;

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (d, 2H), 8.08 (d, 2H), 7.99 (br s, 1H), 7.85 (d, 2H), 7.56 (d, 2H), 7.09 (s, 1H).

Example 94

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-fluorophenyl)benzenemethanamine

Example (vii)-a A was processed as in Example (vii)-a (Method 13) to provide the title compound.

mp 102-103 °C;

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 189-191 °C;
MS(DCI/NH_3) 477 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.40 (br s, 1H), 7.99 (d, 2H), 7.83 (s, 1H), 7.67-7.55 (m, 3H), 7.12 (d, 2H), 3.86 (s, 3H), 3.85 (s, 3H).

Example 99

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopentanepropanamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 130-132 °C;
MS (DCI/NH_3) 437 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.24 (br s, 1H), 7.80 (s, 1H), 7.79 (d, 2H), 7.53 (d, 2H), 2.37 (t, 2H), 1.81-1.73 (m, 3H), 1.66-1.48 (m, 8H).

Example 100

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylbenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 225-226 °C;
MS (DCI/NH_3) 431 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.50 (br s, 1H), 8.01 (d, 2H), 7.91 (d, 2H), 7.83 (s, 1H), 7.61 (d, 2H), 7.37 (d, 2H), 2.40 (s, 3H).

Example 101

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(trifluoromethyl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 143-145 °C;
MS(DCI/NH_3) 485 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.80 (br s, 1H), 8.30 (m, 2H), 8.01 (d, 2H), 7.99 (s, 1H), 7.85-7.80 (m, 2H), 7.65 (d, 2H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.42 (s, 1H), 7.88 (d, 2H), 7.82 (s, 1H), 7.60 (d, 2H), 2.68 (s, 3H), 2.57 (s, 3H).

Example 106

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 185-188 °C;

MS (DCI/NH_3) m/e 401 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.78 (br s, 1H), 9.14 (d, 1H), 8.80 (dd, 1H), 8.32 (dt, 1H,), 8.01 (d, 2H), 7.83 (s, 1H), 7.65-7.58 (m, 3H).

Example 107

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(hydroxymethyl)benzamide

To a solution of carboxylic acid methyl ester, Example142, in toluene was added 1.2 equivalent of DIBAl-H (1.5 M solution in toluene) at -78 °C. After stirring at -78 °C for 1 h, 1 equivalent more of DIBAl-H was added to consume all the starting material. Then the reaction mixtured was quenched with methanol followed by 1N NaOH. After stirring for 30 min, the reaction mixture was partitioned between ether and brine. The organic layer was separated, dried and concentrated to give crude material which was purified by normal phase HPLC (20:80, acetone:hexane). The desired product was collected in approximately 15% yield.

mp 213-214 °C;

MS (ESI-) m/e 428 $(M-H)^-$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.52 (s, 1H), 8.01 (d, 2H), 7.96 (d, 2H), 7.81 (s, 1H), 7.6 (d, 2H), 7.5 (d, 2H), 5.35 (t, 1H), 4.6 (d, 2H).

Example 108

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,4-difluorophenyl)benzenemethanamine

Example (vii)-a A was processed as in Example (vii)-a (Method 13) to provide the title compound and Example 97 as a byproduct.

MS (DCI/NH_3) m/e 422 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.8 (s, 1H), 7.6 (s, 4H), 7.1 (m, 1H), 6.8 (m, 1H), 6.6 (m, 1H), 6.2 (m, 1H), 4.4 (d, 2H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.54 (br s, 1H), 7.99 (d, 2H), 7.98 (d, 1H), 7.83 (s, 1H), 7.60 (d, 2H), 6.75-6.71 (m, 1H).

Example 114

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 188-190 °C;

MS (DCI/NH_3) 435 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.80 (br s, 1H), 7.94 (d, 2H), 7.83 (s, 1H), 7.71 (t, 1H), 7.62 (d, 2H), 7.65-7.59 (m, 1H), 7.36 (q, 2H).

Example 115

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-methyl-1,2-benzenedicarboxamide

2-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoic acid (0.02 g, 0.045 mmol) in thionylchloride (1 mL) was heated to reflux for 3h. The excess thionylchloride was removed under reduced pressure.

To the acid chloride (0.023 mmol) in CH_2Cl_2 (1 mL) was added methylamine hydrochloride (4.6 mg, 0.067 mmol) followed by triethylamine (0.019 mL, 0.14 mmol). After stirring at room temperature over night, the reaction mixture was diluted with ether and washed with 1N HCl, saturated $NaHCO_3$ and brine. The solvent was removed, and the crude material was purified on silica gel column, eluting with 20% acetone /hexane to give the title compound.

MS (DCI/NH_3) m/e 474 $(M+NH_4)^+$;

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.98 (s, 1H), 7.98 (d, 1H), 7.87 (d, 2H), 7.58 (m, 2H), 7.48 (m, 3H), 7.05 (s, 1H), 6.18 (bs, 1H), 3.01 (m, 3H).

Example 116

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 156-157 °C;

MS (DCI/NH_3) m/e 401 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.29 (br s, 1H), 7.84 (d, 2H), 7.73 (s, 1H), 7.56 (d, 2H), 2.90-2.70 (m, 3H), 2.63-2.50 (m, 2H), 1.90-1.80 (m, 2H), 1.63-1.40 (m, 2H), 1.44 (s, 9H).

Example 121

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 401 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.03 (br s, 1H), 8.78 (dd, 1H), 8.21-8.07 (m, 2H), 8.16 (d, 2H), 7.83 (s, 1H), 7.74-7.69 (m, 1H), 7.63 (d, 2H).

Example 122

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(diethylamino)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 471 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.15 (br s, 1H), 7.99 (d, 2H), 7.87 (s, 1H), 7.83 (d, 2H), 7.56 (d, 2H), 6.74 (d, 2H), 3.43 (q, 4H), 1.13 (t, 6H).

Example 123

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopentanecarboxmide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 165-168 °C;

MS (DCI/NH_3) m/e 409 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.22 (br s, 1H), 7.80 (d, 2H), 7.80 (s, 1H), 7.53 (d, 2H), 2.84-2.76 (m, 1H), 1.89-1.54 (m, 8H).

Example 124

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclohexanecarboxmide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 171-173 °C;

MS (DCI/NH_3) m/e 423 $(M+NH_4)^+$;

mp 194-195 °C;
MS (DCI/NH_3) m/e 495 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.5 (s, 1H), 8.32 (d, 1H), 8.17 (d, 1H), 8.0 (d, 2H), 7.86 (t, 1H), 7.84 (s, 1H), 7.65 (d, 2H), 3.3 (s, 3H).

Example 127

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(trifluoromethyl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 133-135 °C;
MS (DCI/NH_3) m/e 485 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.86 (s, 1H), 7.93-7.67 (m, 8H), 7.57 (d, 1H).

Example 128

3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile

Example (vii)-a A was processed as in Example (vii)-a (Method 13) to provide the title compound.
MS (DCI/NH_3) m/e 428 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.8 (s, 1H), 7.6 (m, 4H), 7.2 (m, 1H), 6.9 (m, 4H), 4.4 (d, 2H).

Example 129

Methyl 3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoate

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 174-175 °C;
MS (DCI/NH_3) m/e 475 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) 10.8 (s, 1H), 8.56 (s, 1H), 8.27 (d, 1H), 8.2 (d, 1H), 8.02 (d, 2H), 7.85 (s, 1H), 7.73 (t, 1H), 7.63 (d, 2H), 3.94 (s, 3H).

Example 130

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chlorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

Example 134

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,5-dinitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp >230 °C;

MS (DCI/NH_3) m/e 506 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.17 (s, 1H), 9.20 (d, 2H), 9.03 (t, 1H), 8.03 (d, 2H), 7.85 (s, 1H), 7.70 (d, 2H).

Example 135

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-difluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 126-128 °C;

MS (DCI/NH_3) m/e 453 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.79 (s, 1H), 7.92 (d, 2H), 7.84 (s, 1H), 7.80 (t, 1H), 7.62 (d, 2H), 7.48 (t, 1H), 7.26 (t, 1H).

Example 136

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 174-176 °C;

MS (DCI/NH_3) m/e 462 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.05 (s, 1H), 8.20 (dd, 1H), 7.93-7.75 (m, 6H), 7.63 (d, 2H).

Example 137

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyanobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 162-163 °C;

MS (DCI/NH_3) m/e 442 $(M+NH_4)^+$;

of saturated ammonia in methanol (2 mL) was added. The resulting white solid was filtered and washed with hexane to provide 80 mg (40%) of the desired compound.
mp 177-178 °C;
MS(DCI/NH_3) 496 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.41 (s, 1H), 8.21 (d, 1H), 8.06-7.99 (m, 1H), 8.00 (d, 2H), 7.84 (s, 1H), 7.78 (t, 1H), 7.64 (d, 2H), 7.52 (br s, 2H).

Example 142

methyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoate

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 195-196 °C;
MS (DCI/NH_3) m/e 475 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.12 (m, 4H), 8.0 (d, 2H), 7.84 (s, 1H), 7.63 (d, 2H), 3.92 (s, 3H).

Example 143

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxybenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 100-102 °C;
MS (DCI/NH_3) m/e 447 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.47 (s, 1H), 7.95 (d, 2H), 7.82 (s, 1H), 7.60 (d, 2H), 7.63 (dd, 1H), 7.53 (dt, 1H), 7.20 (d, 1H), 7.07 (t, 1H), 3.91 (s, 3H).

Example 144

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-bromobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 158-160 °C;
MS (DCI/NH_3) m/e 497 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.67 (s, 1H), 8.17 (t, 1H), 8.01 (d, 2H), 8.02-7.86 (m, 1H), 7.82 (s, 1H), 7.84-7.82 (m, 1H), 7.62 (d, 2H), 7.54 (t, 1H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.39 (s, 1H), 7.98 (d, 2H), 7.82 (s, 1H), 7.60 (m, 2H), 7.54 (d, 1H), 7.09 (d, 2H), 6.18 (s, 2H).

Example 149

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 115-117 °C;

MS (DCI/NH_3) m/e 486 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.25 (d, 1H), 7.90 (d, 2H), 7.84 (s, 1H), 7.78 (d, 1H), 7.66 (d, 2H).

Example 150

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 145-147 °C;

MS (DCI/NH_3) m/e 452 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.03 (s, 1H), 8.57 (dd, 1H), 8.16 (dd, 1H), 7.91 (d, 2H), 7.82 (s, 1H), 7.64 (d, 2H), 7.60 (dd, 1H).

Example 151

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-6-methyl-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 155-156 °C;

MS (DCI/NH_3) m/e 466 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.96 (s, 1H), 8.02 (d, 1H), 7.90 (d, 2H), 7.83 (s, 1H), 7.62 (d, 2H), 7.44 (d, 1H), 2.55 (s, 3H).

Example 152

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-γ-oxobenzenebutanamide

Example 156

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]acetamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 169-170 °C;

MS (DCI/NH_3) m/e 355 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.27 (s, 1H), 7.78 (d, 2H), 7.79 (s, 1H), 7.55 (d, 2H), 2.11 (s, 3H).

Example 157

4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoic acid A solution of carboxylic acid methyl ester, Example 142, and 2.5 equivalent of NaOH in ethanol was stirred at 80 °C for 3 hours Then the reaction mixture was diluted with water and acidified with 1N HCl to give the precipitated product.

mp 282-283 °C;

MS (DCI/NH_3) m/e 461 $(M+NH_4)^+$;

^1H NMR (DMSO-D_6, 300 MHz) δ 10.75 (s, 1H), 8.09 (s, 4H), 8.02 (d, 2H), 7.84 (s, 1H), 7.63 (d, 2H).

Example 158

phenylmethyl N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-4-oxobutyl]carbamate

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 532 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.23 (s, 1H), 7.78 (d, 2H), 8.00 (d, 1H), 7.52 (d, 2H), 7.34 (s, 1H), 7.40-7.25 (m, 4H), 5.00 (s, 2H), 3.08 (q, 2H), 2.38 (t, 2H), 1.78 (quintet, 2H).

Example 159

3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoic acid

A solution of Example 129 and NaOH (2.5 equivalents) in ethanol at 80° C was stirred for 3 hours, diluted with water, acidified with 1M HCl, filtered and dried under vacuum to provide the title compound.

Example 163 was prepared from Example 136 using the reduction procedure described in Example 59.

mp 204-206 °C;

MS (DCI/NH_3) m/e 415 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.32 (s, 1H), 7.95 (d, 2H), 7.82 (s, 1H), 7.67 (d, 1H), 7.58 (d, 2H), 7.23 (t, 1H), 6.78 (d, 1H), 6.62 (t, 1H), 6.37 (s, 2H).

Example 164

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluoro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 110-112 °C;

MS (DCI/NH_3) m/e 436 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.94 (s, 1H), 8.42 (d, 1H), 8.31 (dd, 1H), 7.92 (d, 2H), 7.82 (s, 1H), 7.64 (d, 2H), 7.55 (dd, 1H).

Example 165

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloro-4-(methylsulfonyl)-2-thiophenecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 210-212 °C;

MS (DCI/NH_3) m/e 535 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.84 (s, 1H), 9.94 (s, 1H), 7.82 (d, 2H), 7.75 (s, 1H), 7.55 (d, 2H), 3.30 (s, 3H).

Example 166

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1H-pyrrole-2-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp >240 °C;

MS (DCI/NH_3) m/e 406 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.96 (d, 2H), 7.82 (s, 1H), 7.58 (d, 2H), 7.13 (s, 1H), 7.02 (s, 1H), 6.20 (s, 1H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.92 (s, 1H), 10.44 (s, 1H), 7.84 (s, 1H), 7.81 (d, 2H), 7.63 (d, 1H), 7.53 (d, 2H), 7.36 (d, 1H), 7.28 (d, 1H), 7.08 (td, 1H), 6.98 (td, 1H), 3.78 (s, 2H).

Example 171

(E)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(2-thienyl)-2-propenamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 216-218 °C;

MS (DCI/NH_3) m/e 449 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.95 (d, 1H), 7.90 (d, 2H), 7.82 (s, 1H), 7.64 (t, 1H), 7.63 (d, 1H), 7.58 (d, 2H), 7.42 (d, 1H), 6.68 (d, 1H).

Example 172

N-[4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]pyazinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 183-185 °C;

MS (DCI/NH_3) m/e 419 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.34 (d, 1H), 8.98 (d, 1H), 8.84 (dd, 1H), 8.15 (d, 2H), 7.83 (s, 1H), 7.64 (d, 2H).

Example 173

1,1-Dimethylethyl [[4-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-4-oxobutyl]carbamate

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 481 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.80 (d, 2H), 7.95 (s, 1H), 7.55 (d, 2H), 6.82 (t, 1H), 2.98 (q, 2H), 2.34 (t, 2H), 1.71 (quintet, 2H), 1.38 (s, 9H).

Example 174

1-Acetyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-piperidinecarboxamide

Example 178

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methyl-4-(2-thienylcarbonyl)benzeneacetamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp <100 °C;

MS (DCI/NH_3) m/e 555 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.54 (s, 1H), 8.11 (dd, 1H) 7.85 (dd, 2H), 7.83 (dd, 2H), 7.81 (s, 1H), 7.75 (dd, 1H), 7.60 (d, 2H), 7.55 (d, 2H), 7.28 (dd, 1H), 4.01 (q, 1H), 1.5 (d, 3H).

Example 179

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxy-4-(methythio)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 164-165 °C;

MS (DCI/NH_3) m/e 493 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.35 (s, 1H), 7.95 (d, 2H), 7.82 (s, 1H), 7.65 (d, 1H), 7.59 (d, 2H), 7.03 (d, 1H), 6.96 (dd, 1H), 3.95 (s, 3H), 2.55 (s, 3H).

Example 180

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-hydroxy-3-nitrobenzamide

Example 180A

Example (i)-a B and 3-nitro-4-methoxybenzoic acid were processed as in Example (i)-a (Method 5, 6, or 7) to provide the desired compound.

Example 180B

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-hydroxy-3-nitrobenzamide

A solution of example 180A (1.0 mmol) in toluene (3 mL) at -78 °C was treated dropwise with BBr_3 (1.0M in toluene, 1.5 equivalents for each hydroxyl), stirred at -78 °C for 2 hours and at room temperature for 16 hours, recooled to -78 °C, treated with methanol (1 mL), warmed to room temperature, and concentrated. The residue was filtered through a $MgSO_4$/silica gel plug with 20% acetone in hexanes and further purified by HPLC eluting with 20% acetone in hexanes.

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-4-isoxazolecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 163-167 °C;

MS (DCI/NH_3) m/e 422 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.97 (s, 1H), 8.01 (d, 2H), 7.80 (s, 1H), 7.61 (d, 2H), 6.69 (s, 1H), 2.50 (s, 3H).

Example 185

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-chlorophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 162-164 °C;

MS (DCI/NH_3) m/e 451 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.4 (s, 1H), 8.2 (d, 2H), 7.9 (s, 1H), 7.8 (d, 2H), 7.6 (m, 2H), 7.5-7.3 (m, 2H).

Example 186

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(3-cyanophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 195-196 °C;

MS (DCI/NH_3) m/e 442 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.8 (s, 1H), 8.3 (s, 1H), 8.2 (d, 2H), 8.1 (m, 1H), 7.9 (s, 1H), 7.8 (d, 2H), 7.6 (d, 1H), 7.6 (d, 1H).

Example 187

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,4-difluorophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 176-177 °C;

MS (DCI/NH_3) m/e 453 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.4 (s, 1H), 8.2 (d, 2H), 7.9 (s, 1H), 7.8 (d, 2H), 7.6 (m, 1H), 7.4 (m, 1H), 7.2 (m, 1H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.4 (s, 1H), 8.2 (d, 2H), 7.9 (s, 1H), 7.8 (d, 2H), 7.4 (m, 1H), 7.3 (d, 1H), 7.2 (d, 1H).

Example 192

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2-bromophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 163-165 °C;

MS (DCI/NH_3) m/e 496 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.33 (s, 1H), 8.2 (d, 2H), 7.89 (s, 1H), 7.83 (d, 2H), 7.74 (dd, 1H), 7.58 (dd, 1H), 7.45 (dt, 1H), 7.26 (dt, 1H).

Example 193

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-cyanophenyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 192-193 °C;

MS (DCI/NH_3) m/e 442 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.87 (s, 1H), 8.17 (d, 2H), 8.0 (d, 2H), 7.92 (s, 1H), 7.86 (d, 2H), 7.82 (d, 2H).

Example 194

4-[3,5-Bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-pyridinyl)benzamide

Example (v)-a C was processed as in Example (v)-a (Method 11) to provide the title compound.

mp 234-235 °C;

MS (DCI/NH_3) m/e 401 $(M+H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.77 (s, 1H), 8.78 (d, 2H), 8.34 (d, 2H), 8.25 (d, 2H), 7.94 (s, 1H), 7.9 (d, 2H).

Example 195

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-(trifluoromethyl)-benzamide

Example 199

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-5-nitrobenzamide

Example (i)-b B was processed as in Example (i)-b (Method 5, 6, or 7) to provide the title compound.

mp 147-152 °C;

MS (DCI/NH_3) m/e 496 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.1 (s, 1H), 8.6 (d, 1H), 8.4 (dd, 1H), 8.1 (s, 1H), 7.9-7.8 (m, 3H), 7.6 (t, 1H), 7.2 (d, 1H).

Example 200

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 186-187 °C;

MS (DCI/NH_3) m/e 480 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.84 (s, 1H), 8.78 (dd, 1H), 8.42 (m, 1H), 8.0 (d, 2H), 7.82 (s, 1H), 7.81 (dd, 1H), 7.64 (d, 2H).

Example 201

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 178-179 °C;

MS (DCI/NH_3) m/e 503 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.96 (s, 1H), 7.91 (d, 1H), 7.89 (d, 2H), 7.85 (dd, 1H), 7.83 (s, 1H), 7.72 (dt, 1H), 7.62 (d, 2H).

Example 202

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluorobenzamide

Example (i)-b B was processed as in Example (i)-b (Method 5, 6, or 7) to provide the title compound.

mp 150-152 °C;

MS (DCI/NH_3) m/e 435 $(M+NH_4)^+$;

mp 155-157 °C;
MS (DCI/NH_3) 469 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.92 (d, 2H), 7.83 (s, 1H), 7.90-7.60 (m, 2H), 7.63 (d, 2H), 7.40 (dt, 1H).

Example 207

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-(methylsulfonyl)benzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 219-220 °C;
MS (DCI/NH_3) 529 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.08 (br s, 1H), 8.16 (d, 1H), 8.05-7.95 (m, 2H), 7.96 (d, 2H), 7.84 (s, 1H), 7.65 (d, 2H), 2.38 (s, 3H).

Example 208

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-dichlorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 154-156 °C;
MS(DCI/NH_3) 485 $(M + NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.99 (br s, 1H), 7.98 (d, 2H), 7.87 (s, 2H), 7.72-7.65 (m, 4H).

Example 209

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-difluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 147-149 °C;
MS (DCI/NH_3) m/e 453 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.9 (s, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.7 (m, 1H), 7.6 (d, 2H), 7.5 (m, 1H), 7.4 (m, 1H).

Example 210

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.22 (s, 1H), 7.86 (s, 1H), 7.83 (d, 2H), 7.83-7.74 (m, 3H) 7.63 (d, 2H).

Example 214

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloro-2-fluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 113-116 °C;

MS(DCI/NH_3) 469 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.93 (s, 1H), 7.93 (d, 2H), 7.83 (s, 1H), 7.80 (t, 1H), 7.69 (t, 1H), 7.64 (d, 2H), 7.39 (t, 1H).

Example 215

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-methoxybenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 140-143 °C;

MS (DCI/NH_3) m/e 481 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.7 (s, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.2 (d, 1H), 7.0 (m, 2H), 3.8 (s, 3H).

Example 216

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-3-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 160-161 °C;

MS (DCI/NH_3) m/e 530 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.32 (d, 1H), 8.12 (d, 1H), 7.78 (d, 2H), 7.68 (s, 1H), 7.53 (d, 2H).

Example 217

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-bromo-2-chlorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 197-198 °C;
MS (DCI/NH_3) m/e 525 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.49 (s, 1H), 8.26 (d, 1H), 8.05 (dd, 1H), 7.99 (d, 2H), 7.82 (s, 1H), 7.6 (d, 2H), 7.29 (d, 1H), 3.96 (s, 3H).

Example 222

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-bromo-4-hydroxybenzamide

Example 221 was processed as in Example 180B to provide the title compound.
mp 165-167 °C;
MS (ESI-) m/e 492 $(M-H)^-$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.4 (s, 1H), 8.2 (d, 1H), 7.97 (d, 2H), 7.87 (dd, 1H), 7.81 (s, 1H), 7.59 (d, 2H), 7.07 (d, 1H).

Example 223

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4,5-difluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 149-152 °C;
MS (DCI/NH_3) 487 $(M+NH_4)$;
^1H NMR (DMSO-d_6, 300 MHz) δ10.95 (br s, 1H), 8.00-7.90 (m, 2H), 7.91 (d, 2H), 7.84 (s, 1H), 7.64 (d, 2H).

Example 224

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluorobenzamide

Example (i)-b B was processed as in Example (i)-b (Method 5, 6, or 7) to provide the title compound.
mp 142-143 °C;
MS (DCI/NH_3) m/e 453 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.2 (s, 1H), 8.09 (s, 1H), 7.87 (s, 1H), 7.82 (d, 1H), 7.63 (m, 2H), 7.42 (d, 1H), 7.3 (t, 2H).

Example 225

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4,6-trifluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 183-185 °C;

MS (DCI/NH_3) 471 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.18 (s, 1H), 7.89 (d, 2H), 7.84 (s, 1H), 7.65 (d, 2H), 7.46-7.40 (m, 2H).

Example 230

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluoro-3-nitrobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 187-189 °C;

MS (DCI/NH_3) m/e 498 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.4 (s, 1H), 8.4 (m, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.7 (d, 2H), 7.6 (m, 1H).

Example 231

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,5-trifluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 169-170°C;

MS (DCI/NH_3) m/e 471 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.99 (s, 1H), 7.91 (d, 2H), 7.83 (s, 1H), 7.88-7.78 (m, 1H), 7.64 (d, 2H), 7.58-7.48 (m, 1H).

Example 232

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-dichloro-6-fluorobenzamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 185-188 °C;

MS (DCI/NH_3) m/e 503 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.01 (d, 1H), 7.94-7.85 (m, 3H), 7.82 (s, 1H), 7.62 (d, 2H).

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 188-189°C;
MS (DCI/NH_3) m/e 458 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.12 (d, 1H), 7.92-7.82 (t, 3H), 7.67-7.57 (m, 4H), 3.32 (s, 3H).

Example 238

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide

Example (i)-b B was processed as in Example (i)-b (Method 5, 6, or 7) to provide the title compound.
mp 133-134 °C;
MS (DCI/NH_3) m/e 442 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 0.8 (s, 1H), 8.2-8.0 (m, 5H), 7.9 (d, 1H), 7.8 (s, 1H), 7.6 (t, 1H), 7.4 (d, 1H).

Example 239

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-thiophenecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 239-240 °C;
MS (DCI/NH_3) m/e 423 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.4 (m, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.7-7.6 (m, 2H), 7.6 (d, 2H).

Example 240

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-isoxazolecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 202-204 °C;
MS (DCI/NH_3) m/e 408 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.0 (s, 1H), 8.8 (d, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.3 (d, 1H).

Example 241

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-2-furancarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 113-116 °C;

MS (DCI/NH_3) m/e 411 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.93 (d, 2H), 7.80 (s, 1H), 7.56 (d, 2H), 4.45 (dd, 1H), 4.01 (q, 1H), 3.85 (q, 1H), 2.26-2.17 (m, 1H), 2.07-1.98 (m, 1H), 1.93-1.87 (m, 2H).

Example 242

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyrrolidinecarboxamide

Example 242 was prepared from Example 246 using the procedure described to prepare Example 125.

mp 82-84 °C;

MS (DCI/NH_3) m/e 393 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.30 (s, 1H), 7.90 (d, 2H), 7.82 (s, 1H), 7.55 (d, 2H), 3.76-3.74 (dd, 1H), 2.93 (t, 2H), 2.14-2.01 (m, 1H), 1.88-1.75 (m, 1H), 1.69 (q, 2H).

Example 243

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-3-furancarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 193-194 °C;

MS (DCI/NH_3) m/e 411 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.70 (s, 1H), 8.18-8.03 (m, 3H), 7.90-7.78 (m, 2H), 4.31-4.18 (m, 1H), 4.17-3.89 (m, 4H), 2.45-2.25 (m, 2H).

Example 244

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 213-214 °C;

MS (DCI/NH_3) m/e 425 $(M+NH_4)^+$;

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 148-149 °C;
MS (DCI/NH_3) m/e 420 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.0 (s, 1H), 7.9 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 7.1 (m, 2H), 6.1 (dd, 1H), 3.9 (s, 3H).

Example 249

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-6-chloro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 192-194 °C;
MS (DCI/NH_3) m/e 452 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.79 (s, 1H), 8.98 (d, 1H), 8.37 (dd, 1H), 7.97 (d, 2H), 7.82 (s, 1H), 7.73 (d, 1H), 7.64 (d, 2H).

Example 250

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1,2,3-thiadizole-5-carboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 164-166 °C;
MS (ESI-) m/e 420 $(M-H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.06 (s, 1H), 7.92 (d, 2H,), 7.84 (s, 1H), 7.66 (d, 2H), 2.84 (s, 3H).

Example 251

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-bromo-2-furancarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 181-182 °C;
MS (DCI/NH_3) m/e 486 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.96 (d, 2H), 7.82 (s, 1H), 7.61 (d, 2H), 7.44 (d, 1H), 6.88 (d, 1H).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.94 (s, 1H), 7.86 (d, 2H), 7.81 (s, 1H), 7.58 (d, 2H), 4.27 (m, 1H), 2.38 (m, 1H), 2.2 (m, 2H), 2.05 (m, 1H).

Example 256

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-bromo-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 155-157 °C;

MS (DCI/NH_3) m/e 489 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.8 (s, 1H), 9.1 (d, 1H), 8.9 (d, 1H), 8.6 (t, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H).

Example 257

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-nitro-3-thiophenecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 164-165 °C;

MS (DCI/NH_3) m/e 468 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.7 (d, 1H), 8.6 (d, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H).

Example 258

1,1-Dimethylethyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]-3-thiazolidinecarboxylate

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 82-84 °C;

MS (DCI/NH_3) m/e 528 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.45 (s, 1H), 7.82 (s, 1H), 7.80 (d, 2H), 7.58 (d, 2H), 4.68-4.42 (m, 3H), 3.58-3.43 (m, 1H), 3.24-3.15 (m, 1H), 1.30 (s, 9H).

Example 259

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methoxy-3-thiophenecarboxamide

Example 263

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-dibromo-5-thiophenecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 142-144 °C;

MS (DCI/NH_3) m/e 581 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.66 (s, 1H), 8.13 (s, 1H), 7.95 (d, 2H), 7.85 (s, 1H), 7.65 (d, 2H).

Example 264

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-fluoro-4-pyridinecarboxamide

The procedure described by Shi, G.; Takagishi, S.; Schlosser, M. *Tetrahetron*. **1994**, *50*, 1129-1134 and Lecomte, L.; Ndzi, B.; Queguiner, G.; Turck, A. FR. 2,686,340-A1, hereby incorporated by reference, was used. Under reduced pressure, the volatile components were stripped off from a solution of n-butyllithium (30 mL) in hexanes. At -78 °C, potassium tert-butoxide (2.75 g, 25 mmol), THF (30 mL), and a precooled solution of 3-fluoropyridine (2.5 g 25 mmol, 2.18 mL) in THF (30 mL) were consecutively added to the residue with stirring until the alcoholate dissolved. After 4 hours at -78 °C, the reaction mixture was poured onto fresh dry ice. After evaporation to dryness, the solid salt was treated with a small excess of 1M hydrogen chloride in diethyl ether. Then the mixture (desired product in hydrochloric salt form and KCl salt) was concentrated to give 2.0 g of a brown solid. This mixure was used in the coupling procedure described below in which a small amount of pyridine was used to neutralize the acidic salt form.

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound using the isofluoronicotinic acid prepared as described in the preceding paragraph.

mp 152-153 °C;

MS (DCI/NH_3) m/e 436 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.80 (s, 1H), 8.63 (dd, 1H), 7.83 (d, 2H), 7.84 (s, 1H), 7.77 (t, 1H), 7.64 (d, 2H).

Example 265

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-1H-pyrazole-4-carboxamide

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.43 (s, 1H), 8.06 (s, 1H), 7.93 (d, 2H), 7.84 (s, 1H), 7.6 (d, 2H), 3.93 (s, 3H).

Example 268

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5,6-dichloro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 175-177 °C;

MS (DCI/NH_3) m/e 486 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.0 (d, 1H), 8.6 (d, 1H), 8.0 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H).

Example 269

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-4-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 215-216 °C;

MS (DCI/NH_3) m/e 486 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.92 (s, 1H), 8.04 (s, 2H), 7.97 (d, 2H), 7.84 (s, 1H), 7.67 (d, 2H).

Example 270

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-dichloro-3-pyridinecarboxamide

Example (i)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 228-229 °C;

MS (DCI/NH_3) m/e 487 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.70 (d, 1H), 8.45 (d, 1H), 7.88 (d, 2H), 7.83 (s, 1H), 7.64 (d, 2H).

Example 271

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4-chlorobenzamide

MS (DCI/NH_3) m/e 589 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.17 (s, 1H), 8.52 (d, 1H), 8.08 (dd, 1H), 7.98 (d, 1H), 7.82-7.74 (m, 3H), 7.58 (d, 1H), 3.64 (s, 3H).

Example 275

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-3,5-dimethyl-4-isoxazolecarboxamide

Example (xi)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 61-63 °C;
MS (ESI-) m/e 485 $(M-H)^-$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.68 (s, 1H), 8.38 (d, 1H), 8.11 (dd, 1H,), 7.93 (s, 1H), 7.92 (d, 1H), 2.61 (s, 3H), 2.38 (s, 3H);
Anal. calcd for $C_{18}H_{11}F_9N_4O_2$: C, 44.45; H, 2.28; N, 11.52. Found: C, 44.60; H, 2.37; N, 10.91.

Example 276

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-(trifluoromethyl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example (xi)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 134-136 °C;
MS (ESI-) m/e 488 $(M-H)^-$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.35 (s, 1H), 8.18 (d, 1H), 8.16 (dd, 1H), 7.96 (d, 1H), 7.94 (s, 1H), 2.86 (s, 3H);
Anal. calcd for $C_{16}H_8F_9N_5OS$: C, 39.27; H, 1.68; N, 14.18. Found: C, 39.29; H, 1.71; N, 13.81.

Example 277

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-3-chlorophenyl]-3,5-dimethyl-4-isoxazolecarboxamide

Example (xiii)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 64-65 °C;

Example (xv)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 119-121 °C;
MS (ESI-) m/e 450 $(M-H)^-$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.14 (d, 1H); 7.94 (s, 1H), 7.75 (d, 1H), 7.23 (dd, 1H), 3.97 (s, 3H), 2.85 (s, 3H);
Anal. calcd for $C_{16}H_{11}F_6N_5O_2S$: C, 42.57; H, 2.45; N, 15.51. Found: C, 43.19; H, 2.46; N, 14.46.

Example 281

4-chloro-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide

Example (xix)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 145-146 °C;
MS (DCI/NH_3) m/e 370 $(M+H)^+$;
^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H), 7.78 (d, 2H), 7.49 (d, 2H), 7.47 (d, 2H), 6.67 (s, 1H), 2.36 (s, 3H).

Example 282

4-methyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide

Example (xix)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 51-53 °C;
MS (DCI/NH_3) m/e 368 $(M+H)^+$;
^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H), 7.78 (d, 2H), 7.49 (d, 2H), 7.47 (d, 2H), 6.67 (s, 1H), 2.36 (s, 3H).

Example 283

3,5-Dimethyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-isoxazolecarboxamide

Example (xix)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 180-181 °C;

Example (xxii)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 177-178 °C;

MS (DCI/NH_3) m/e 351 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.24 (s, 1H), 8.69 (d, 1H), 7.86 (dd, 4H), 7.04 (d, 1H), 2.57 (s, 3H), 2.36 (s, 3H).

Example 288

N-[4-[5-hydroxy-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example (xxiii)-a C was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 177- 179 °C;

MS (ESI-) m/e 368 $(M-H)^-$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.87 (s, 1H), 8.82 (d, 2H), 8.67 (d, 2H), 5.82 (s, 1H), 2.84 (s, 3H).

Example 289

N-[4-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example (xxv)-a B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 144-145 °C;

MS (DCI/NH_3) m/e 315 $(M+H)^+$;

^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 2H), 7.28 (d, 2H), 3.01 (s, 3H), 2.51 (s, 3H), 2.42 (s, 3H).

Example 290

3-amino-N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 290A

3-nitro-nicotinic acid

3-Nitro-4-methylpyridine (2 g, 14 mmol) in water (200 mL) was refluxed while a saturated solution of potassium permanganate (4.43 g, 28 mmol) in water (20 mL) was added dropwise over a 4 hour period. At the end of addition, the solution was refluxed for another

Example (i)-a B was processed as described in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 187-188 °C;
MS (DCI/NH_3) m/e 482 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.81 (s, 1H), 7.98 (d, 2H), 7.85 (s, 1H), 7.65 (d, 2H), 7.58 (s, 1H), 7.35 (s, 1H), 3.95 (s, 3H).

Example 292

N-(6-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-3-pyridinyl)-2-fluorobenzamide

Example 292A

5-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-2-nitropyridine

To a cold slurry (0°C) of sodium hydride (95%, 160 mg, 6.67 mmol) in dimethylformamide (10 mL) was added 3,5-bis(trifluoromethyl)pyrazole (1.12g, 5.50 mmol). The resulting suspension was stirred for 30 minutes. A solution of 2-chloro-4-nitropyridine (867 mg, 5.5 mmol) was added. The resulting mixture was heated at reflux for 12 hours, then cooled to room temperature. The mixture was poured into saturated sodium chloride solution (100 mL). The aqueous mixture was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography using 20% ethyl acetate/hexane to afford a yellow oil (1.78 g, 99% yield).
MS (DCI/NH_3) m/e 326 $(M + H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 9.39 (d, 1H), 8.86 (dd, 1H), 8.21 (d, 1H), 8.02 (s, 1H).

Example 292B

5-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-2-pyridinylamine

To a a slurry of 10% palladium on carbon (192 mg) in ethyl acetate (90 mL) under a nitrogen atmosphere was added a solution of Example 292A (1.77 g, 5.43 mmol) in ethyl acetate (10 mL). A hydrogen balloon was placed on the reaction flask and the reaction mixture was maintained under a hydrogen atmosphere for 20 hours. The reaction flask was purged with nitrogen and then the catalyst was filtered off through a diatomaceous earth/silica gel plug to afford an oil (1.20g, 75% yield).
MS (DCI/NH_3) m/e 297 $(M + H)^+$;

The nitro group of Example 293A was reduced with iron powder and ammonium chloride as described in Example 355B..
mp 45-47°C;
MS (DCI/NH_3) m/e 371 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.6 (s, H), 7.20 (d, 1H, J=6 Hz), 6.76 (dd, 1H, J=9,3 Hz), 5.92 (s, 2H), 3.46 (s, 3H).

Example 293

methyl 2-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-5-((2-fluorobenzoyl)amino)benzoate

Example 293 B was processed as in Method 5 or 6, or 7 to provide the title compound.
MS (DCI/NH_3) m/e 493 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.54 (d, 1H), 8.16 (dd, 1H), 7.80 (d, 1H), 7.76 (td, 1H), 7.69-7.60 (m, 1H), 7.45-7.35 (m, 2H), 3.65 (s, 3H).

Example 294

4-(aminomethyl)-N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-chlorobenzamide

Example 294A

4-cyano-2-chlorobenzoic acid

Under a nitrogen atmosphere, $Zn(CN)_2$ (58 mg, 0.50 mmol) and 4-bromo-2-chlorobenzoic acid (200 mg, 0.90 mmol) were added to dry dimethylformamide (5 mL), followed by tetrakis(triphenylphosphine)palladium(0) (43 mg, 0.036 mmol). The resulting yellow slurry was heated to 80 °C overnight. After it was cooled to room temperature, it was diluted with ethyl ether (20 mL), and washed with water (2 X 10 mL). Then the ethereal portion was collected, dried with Na_2SO_4, filtered and concentrated in vacuo to give 2-chloro-4-cyanobenzoic acid (60 mg, 37% yield) as a white solid.

Reference: Magidson, O.J.; Trawin, A.I. *Chem Ber.* **1936**, *69*, 537-544.

Example 294B

N-{4-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}-2-chloro-4-cyanobenzamide

Example (i)-a B and Example 294A were processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
MS (DCI/NH_3) m/e 476 $(M+NH_4)^+$

^{1}HNMR (300 MHz, $CDCl_3$) δ 8.53 (d, 1H, J=16.2 Hz), 8.16 (dd, 1H, J=8.7, 8.4Hz), 7.84 (m, 2H), 7.52 (m, 2H), 7.35 (dd, 1H, J=8.4, 1.8 Hz), 7.27 (dd, 1H, J=12.0, 1.8 Hz), 7.08 (s, 1H).
Anal. Calcd for $C_{18}H_9ClF_7N_3O$: C, 47.86; H, 2.01; N, 9.30. Found: C, 48.14; H, 2.05; N, 9.11.

Example 297

N-(5-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-2-pyridinyl)-2-fluorobenzamide

Example 297A

5-chloro-2-nitropyridine

To cold (0 °C) concentrated sulfuric acid (80 mL) was added 30% hydrogen peroxide (40 mL). To this solution was added 2-amino-5-chloropyridine (4.00 g, 31.11 mmol). The solution became lime colored within 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours. The reaction mixture was then poured into ice water and a white precipitate formed. This solid was filtered and dried in vacuo to afford 5-chloro-2-nitropyridine (3.10 g, 63% yield).
MS (DCI/NH_3) m/e 129 (M+H for aniline)$^+$;
^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.78 (m, 1H), 8.37 (m, 2H).

Example 297B

5-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-nitropyridine

To a cold slurry (0 °C) of sodium hydride (95%, 439 mg, 18.30 mmol) in dimethylformamide 3.0 mL) was added 3,5-bis(trifluoromethyl)pyrazole (2.50 g, 12.30 mmol). The resulting suspension was stirred for 30 minutes. A solution of 5-chloro-2-nitropyridine (1.90 g, 12.00 mmol) was added. The resulting mixture was heated at reflux for 24 hours, then cooled to room temperature. The mixture was poured into saturated sodium chloride solution (100 mL). The aqueous mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography using 20% ethyl acetate/hexane to afford a yellow oil (1.17 g, 30% yield).
MS (DCI/NH_3) m/e 297 (M+1 for aniline)$^+$;
^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.38 (d, 1H), 8.88 (dd, 1H), 8.21 (d, 1H), 8.02 (s, 1H).

Example 297C

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.72 (d, 1H), 8.60 (dd, 1H), 8.09 (dd, 1H), 7.88 (s, 1H).

Example 298B

2-(trimethylsilyl)ethyl 2-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-5-nitrophenylcarbamate

A mixture of Example 298A (421 mg, 1.23 mmol), triethylamine (1.0 mL, 6.15 mmol), diphenylphosphorylazide (0.40 mL, 1.85 mmol) and β-trimethylsilylethanol (0.88 mL, 6.15 mmol) in toluene was heated at 70 °C for 20 hours. The reaction mixture was cooled and concentrated in vacuo. Purification of the crude residue with flash chromatography eluting with 10% ethyl acetate/hexane affored the title compound (230 mg, 39% yield) as a yellow oil.

MS (DCI/NH_3) m/e 502 $(M + NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.82 (s, 1H), 8.81 (d, 1H), 8.03 (dd, 1H), 7.85 (s, 1H), 7.75 (d, 1H), 4.09 (t, 2H), 0.95 (t, 2H), 0.02 (s, 9H).

Example 298C

2-(trimethylsilyl)ethyl 5-amino-2-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenylcarbamate

Example 298B was reduced using general hydrogenation method described in method 4.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.71 (s, 1H), 7.60 (s, 1H), 6.99 (dd, 1H), 6.38 (dd, 1H), 5.68 (s, 2H), 4.03 (t, 2H), 0.91 (t, 2H), 0.02 (s, 9H).

Example 298D

2-(trimethylsilyl)ethyl 2-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-5-[(2-fluorobenzoyl)amino]phenylcarbamate

Example 298C was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 594 $(M + NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.78 (s, 1H), 9.24 (s, 1H), 8.25 (d, 1H), 7.74 (s, 1H), 7.65 (m, 3H), 7.38 (m, 3H), 4.05 (t, 2H), 0.95 (t, 2H), 0.02 (s, 9H).

Example 298

N-{3-amino-4-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}-2-fluorobenzamide

Example 299B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 132-134°C;

MS (DCI/NH_3) m/e 460 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.15 (s, 1H), 8.58 (d, 1H), 8.47 (d, 1H), 8.20 (dd, 1H), 8.04 (s, 1H), 7.47-8.28 (m, 4H).

Example 300

N-{4-[5-cyano-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}-2-fluorobenzamide

Example 300A

2,2,2-trifluoroacetaldehyde *N*-(4-nitrophenyl)hydrazone

A 1L round bottom flask equipped with a stir bar and a 250 mL pressure equalizing dropping funnel was charged with trifluoroacetic acid (10.0 mL, 130 mmol) and ether (350 mL). To this cold solution (0 °C) solution was added lithium aluminum hydride (1 M soln. in ether, 100 mL, 100 mmol) via the dropping funnel over 20 min. The resulting solution was stirred at 0 °C for 1 h. The reaction was quenched by the addition of methanol (10 mL), followed by water (10 mL), then concentrated HCl (17 mL). The ether layer was extracted with water (300 mL), then dried over sodium sulfate, filtered and concentrated. The crude material was used in the next step without further purification. A mixture of the trifluoroacetaldehyde thus produced (ca. 130 mmol), 4-nitrophenylhydrazine (15.02 g, 98.04 mmol), ethanol (250 mL) and concentrated HCl (5.0 mL) were heated to 100 °C for 2 hours. The reaction was cooled, approximately 90% of the ethanol was removed in vacuo, and then ether (350 mL) was added. The ether layer was washed with saturated sodium bicarbonate solution (300 mL), then dried over sodium sulfate, filtered and concentrated to a crude orange solid (22.8 g, 99%) which was pure enough to use in the next step.

MS (DCI/NH_3) m/e 251 $(M + NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.78 (s, 1H), 8.20 (d, 2H), 7.55 (q, 1H), 7.19 (d, 2H).

Example 300B

2,2,2-trifluoro-*N*-(4-nitrophenyl)ethanehydrazonoyl chloride

To a solution of Example 300A (7.4 g, 0.031 mol) in DMF (30 mL) was added a solution of N-chlorosuccinimide (4.38 g, 0.033 mol, 1.05 eq) in DMF (15 mL) dropwise at 0 ^{0}C. After addition, the resulting dark green mixture was stirred at room temperature for two

N-{4-[5-cyano-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}-3-fluoroisonicotinamide

Example 300D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 161-162 °C;

MS (DCI/NH_3) m/e 393 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.05 (s, 1H), 8.79 (s, 1H), 8.62 (d, 1H), 8.07 (s, 1H), 7.96 (d, 2H), 7.81 (d, 2H), 7.75 (t, 1H);

^{13}C NMR(DMSO-d_6, 75 MHz) δ 161.3, 155.0 (d, J= 259 Hz), 146.4, 142.0 (q, J = 39 Hz), 139.9, 139.0 (d, J = 23 Hz), 133.1, 131.2 (d, J = 14 Hz), 124.9, 123.2, 120.5 (q, J = 262 Hz), 120.5, 116.7, 114.7, 109.9.

Anal. calcd for $C_{17}H_9F_4N_5O$: C, 54.40; H, 2.41; N, 18.66. Found: C, 54.47; H, 2.52; N, 18.49.

Example 301

2-fluoro-N-(4-(5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide

Example 301A

5-(2-furyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole

4-Nitrophenylhydrazine (7.75 g, 50.5 mmol) in a mixture of absolute ethanol (75 mL) and concentrated HCl (40 mL) was treated with 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (12.5 g, 60.6 mmol) and heated to reflux for 2 hours. The reaction mixture was cooled to room temperature and diluted with hexanes/ethyl acetate (600 mL of a 1:1 mixture). The layers were separated, and the organic layer was washed with 1.0 N HCl (3 x 100 mL) and then saturated brine solution. The resultant mixture was dried over Na_2SO_4, and concentrated in vacuo. Purification using silica gel chromatography (97:3 hexanes/ethyl acetate gradient to 95:5 hexanes/ethyl acetate) yielded a white amorphous solid (14.7 g, 90% yield).

^{1}HNMR (300 MHz, $CDCl_3$) δ 8.33 (dt, 2H, J=9.3,2.7Hz), 7.62 (dt, 2H, J=9.0,2.7Hz), 7.45 (dd, 1H, J=1.5, 0.6Hz), 6.92 (s, 1H), 6.47 (dd, 1H, J=3.6,1.5Hz), 6.39 (dd, 1H, J=3.3,0.6Hz).

Example 301B

4-[5-(2-furyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

A solution of Example 301A (1.2 g, 3.7 mmol) in isopropanol (80 mL) was treated with 10% Pd/C (400 mg) and placed under a hydrogen atmosphere (balloon). After 1.75 hours the reaction was complete and the mixture was filtered through a plug of diatomaceous

Example 304

N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 300D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 161-162 °C;

MS (DCI/NH_3) m/e 393 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.05 (s, 1H), 8.79 (s, 1H), 8.62 (d, 1H), 8.07 (s, 1H), 7.96 (d, 2H), 7.81 (d, 2H), 7.75 (t, 1H);

^{13}C NMR(DMSO-d_6, 75 MHz) δ 161.3, 155.0 (d, J= 259 Hz), 146.4, 142.0 (q, J = 39 Hz), 139.9, 139.0 (d, J = 23 Hz), 133.1, 131.2 (d, J = 14 Hz), 124.9, 123.2, 120.5 (q, J = 262 Hz), 120.5, 116.7, 114.7, 109.9.

Anal. calcd for $C_{17}H_9F_4N_5O$: C, 54.40; H, 2.41; N, 18.66. Found: C, 54.47; H, 2.52; N, 18.49.

Example 305

N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide

Example 305A

1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxylic acid

Example 301A (3.7 g, 11.6 mmol) in a mixture of *tert*-butanol (65 mL) and 0.5 N NaOH (35 mL) was treated with $KMnO_4$ (4.5 g, 28.5 mmol) and heated at 75 °C for 1 hour. The mixture was cooled to ambient temperature, and the second portion of $KMnO_4$ (4.5 g, 28.5 mmol) was added. After stirring for an additional 1 hour at 75 °C, the reaction mixture was cooled to ambient temperature and filtered through a thick plug of diatomaceous earth. The diatomaceous earth was washed with water (3 x 100 mL). The combined washes were concentrated to 50% of the original volume and acidified to pH=3 with 50% HCl solution. Next, the mixture was extracted with ethyl acetate (3 x 100 mL) and the combined extracts were dried over Na_2SO_4, and concentrated in vacuo. Purification using silica gel chromatography (75:20:5 hexanes/ethyl acetate/acetic acid gradient to 55:35:10 hexanes/ethyl acetate/acetic acid) yielded a white amorphous solid (1.8 g, 51% yield) along with 1.3 g of the corresponding ketoacid intermediate. The ketoacid intermediate was resubmitted to the conditions above to produce additional carboxylic acid (300 mg, yield after resubmission 60%, unoptimized).

MS (ESI-) m/e 300 $(M-1)^-$;

The mixture was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to yield a white foam (36 mg, 75% yield). MS (ESI+) m/e 270 $(M+1)^+$;
^{1}HNMR (300 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.06 (ddd, 2H, J=8.4, 3.0, 2.1Hz), 6.58 (ddd, 2H, J=8.7, 3.0, 2.1Hz), 5.47 (s, 2H), 2.49 (s, 3H).

Example 305

N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide

Example 305 D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 188-189 °C;
MS (ESI+) m/e 393 $(M+1)^+$;
^{1}HNMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.78 (d, 1H, J=1.6Hz), 8.62 (dd, 1H, J=4.8, 1.2Hz), 7.86 (s, 1H), 7.82 (ddd, 2H, J=8.8, 6.8, 2.8Hz), 7.74 (t, 1H, J=5.3Hz), 7.50 (ddd, 2H, J=8.8, 7.2, 3.2Hz), 2.57 (s, 3H);
^{13}CNMR (100 MHz, DMSO- d_6) δ 187.8, 161.0, 156.3, 153.7, 146.4, 141.2, 141.0, 140.6, 139.0, 138.9, 135.4, 131.4, 131.2, 126.5, 123.2, 122.2, 119.7, 119.6, 111.1, 28.8;
Anal. calcd for $C_{18}H_{12}F_4N_4O_2$: C, 55.11; H, 3.08; N, 14.28. Found: C, 55.05; H, 3.33; N, 13.71.

Example 306

N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide

Example 300D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 150-151°C;
MS (DCI/NH_3) m/e 393 $(M+NH_4)^+$;
^{1}H NMR (DMSO-d6, 300 MHz) δ 10.96 (s, 1H), 8.44 (d, 1H), 8.30 (td, 1H), 8.09 (s, 1H), 7.97 (d, 2H), 7.82 (d, 2H), 7.59-7.52 (m, 1H).

Example 307

N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2,3,5-trifluorobenzamide

Example 300D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
MS (DCI/NH_3) m/e 428 $(M + NH4)^+$;

MS (DCI/NH_3) m/e 449 $(M+NH_4)^+$; 432 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.75 (s, 1H), 7.9 (d, 2H), 7.75-7.65 (m, 1H), 7.7 (dd, 1H), 7.65-7.55 (m, 1H), 7.5 (d, 2H), 7.45-7.30 (m, 2H), 7.3 (s, 1H), 7.25 (dd, 1H), 7.1 (m, 1H).

Example 309

2-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide

Examples 309A-1 and 309A-2

5-(methylsulfanyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole

and

1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ol

S-Methyl 4,4,4-trifluoro-3-oxothiobutyrate (2.76 mL, 0.02 mol) and p-nitrophenylhydrazine (3.06 g, 0.02 mol) were dissolved in ethanol 18 mL and 4M HCl/dioxane (18 mL). The solution was refluxed overnight. After cooling the reaction mixture to room temperature, it was partitioned between ether and water. The ether layer was extracted with saturated aquesous $NaHCO_3$ (3x), washed with brine, dried over Na_2SO_4 and evaporated to give 5-(methylsulfanyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (Example 309A-1, 0.61 g, 10% yield). The $NaHCO_3$ extractions were combined and washed with ether. The $NaHCO_3$ solution was then acidified with 1N HCl to pH~5 and extracted with ether (3x). The ether extracts were combined, dried over Na_2SO_4 and concentrated to give 1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ol (Example 309A-2, 4.02 g, 74% yield).

Example 309A-1:

MS (DCI/NH_3) m/e 304 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.44 (d, 2H), 7.94 (d, 2H), 7.18 (s, 1H), 2.6 (s, 3H).

Example 309A-2:

MS (DCI/NH_3) m/e 291 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.39 (d, 2H), 8.1 (d, 2H), 6.0 (s, 1H).

Example 309B

4-[5-(methylsulfanyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

Example 309A-1 was reduced with Fe powder as described previously to gave the title compound in 75% yield.

MS (DCI/NH_3) m/e 291$(M+NH_4)^+$;

Example 310B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 138-140 °C;
MS (DCI/NH_3) m/e 427 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.7 (s, 1H), 8.6-8.6 (m, 2H), 7.8 (d, 2H), 7.7-7.65 (m, 2H), 7.65-7.55 (m, 1H), 7.45-7.3 (m, 6H).

Example 311

3-fluoro-N-(4-(5-(2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 308B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 153-155 °C;
MS (DCI/NH_3) m/e 433 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.0 (s, 1H), 8.8 (s, 1H), 8.6 (d, 1H), 7.9 (d, 2H), 7.75 (t, 1H), 7.6 (d, 1H), 7.5 (d, 2H), 7.3 (s, 1H), 7.25 (d, 1H), 7.1 (m, 1H).

Example 312

N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 312A

methyl 1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl ether

To a mixture of Example 309A-2 (0.776 g, 2.84 mmol) and K_2CO_3 (0.94 g, 6.8 mmol) in acetonitrile (10 mL) was added dimethyl sulfate (0.32 mL, 3.4 mmol). Then the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ether and washed with brine. After evaporation of the solvent, the crude was passed through short silica gel plug eluting with methylene chloride to give the title compound (0.71 g, 88% yield).
MS (DCI/NH_3) m/e 305 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.39 (d, 2H), 8.03 (d, 2H), 6.59 (s, 1H), 4.08 (s, 3H).

Example 312B

4-[5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

Reduction of the nitro group of Example 312A with Fe powder gave the title compound in 82% yield.

N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide

Example 305 D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 188-189 °C;

MS (ESI+) m/e 393 $(M+1)^+$;

^{1}HNMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.78 (d, 1H, J=1.6Hz), 8.62 (dd, 1H, J=4.8, 1.2Hz), 7.86 (s, 1H), 7.82 (ddd, 2H, J=8.8, 6.8, 2.8Hz), 7.74 (t, 1H, J=5.3Hz), 7.50 (ddd, 2H, J=8.8, 7.2, 3.2Hz), 2.57 (s, 3H);

^{13}CNMR (100 MHz, DMSO-d_6) δ 187.8, 161.0, 156.3, 153.7, 146.4, 141.2, 141.0, 140.6, 139.0, 138.9, 135.4, 131.4, 131.2, 126.5, 123.2, 122.2, 119.7, 119.6, 111.1, 28.8;

Anal. calcd for $C_{18}H_{12}F_4N_4O_2$: C, 55.11; H, 3.08; N, 14.28. Found: C, 55.05; H, 3.33; N, 13.71.

Example 316

2-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide

Example 309B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 167-168 °C;

MS (DCI/NH_3) m/e 414 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.88 (s, 1H), 8.43 (m, 1H), 8.3 (m, 1H), 7.9 (d, 2H), 7.58 (d, 2H), 7.55 (m, 1H), 7.04 (s, 1H), 2.55 (s, 3H).

Example 317

2-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide

Example 312B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 153-154 °C;

MS (DCI/NH_3) m/e 398 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.78 (s, 1H), 8.42 (m, 1H), 8.29 (m, 1H), 7.86 (d, 2H), 7.66 (d, 2H), 7.53 (m, 1H), 6.48 (s, 1H), 4.0 (s, 3H).

Example 318

3-fluoro-N-(4-(3-(4-pyridinyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

4-[5-ethoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

Example 309A-2 was alkylated as described in Example 312A (substituting ethyl bromide for dimethyl sulfate). Yield, 65%. Subsequent reduction with iron powder supplied the aniline. Yield, 71%.

MS (DCI/NH_3) m/e 289 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.18 (d, 2H), 6.62 (d, 2H), 6.34 (s, 1H), 5.4 (s, 2H), 4.23 (q, 2H), 1.34 (t, 3H).

Example 319

N-(4-(5-ethoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide

Example 319A was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 152-153 °C;

MS (DCI/NH_3) m/e 412 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.3 (s, 1H), 8.92 (m, 1H), 8.28 (m, 1H), 7.85 (d, 2H), 7.67 (d, 2H), 7.54 (m, 1H), 6.48 (s, 1H), 4.3 (q, 2H), 1.38 (t, 3H).

Example 320

3-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 309B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 142-143 °C;

MS (DCI/NH_3) m/e 414 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.79 (s, 1H), 8.62 (d, 1H), 7.9 (d, 2H), 7.76 (t, 1H), 7.59 (d, 2H), 7.04 (s, 1H), 2.58 (s, 3H).

Example 321

3-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 312B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 160-161 °C;

MS (DCI/NH_3) m/e 398 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.79 (s, 1H), 8.61 (d, 1H), 7.76 (d, 2H), 7.74 (t, 1H), 7.68 (d, 2H), 6.49 (s, 1H), 4.01 (s, 3H).

MS (DCI/NH_3) m/e 416 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.8 (d, 2H), 7.99 (d, 2H), 7.88 (d, 2H), 7.65 (d, 2H), 7.16-7.64 (t, 1H), 6.84 (s, 1H).

Example 323

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example 322B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 122-123 °C;

MS (DCI/NH_3) m/e 437 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.89 (d, 2H), 7.65 (d, 2H), 7.16-7.64 (t, 1H), 6.84 (s, 1H), 2.84 (s, 3H).

Example 324

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide

Example 322B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 149-150 °C;

MS (DCI/NH_3) m/e 434 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.44 (m, 1H), 8.28 (m, 1H), 7.9 (d, 2H), 7.65 (d, 2H), 7.55 (m, 1H), 7.16-7.64 (t, 1H), 6.84 (s, 1H).

Example 325

N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide

Example 325A

5-chloro-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole

A slurry of Example 309A-2 (4.63 g, 16.9 mmol) in phenylphosphinic dichloride (11.5 mL, 81.1 mmol) was heated to 145 °C for 48 hours in a sealed tube with stirring. The reaction mixture was cooled to room temperature and carefully poured into saturated sodium bicarbonate solution (300 mL). The aqueous layer was further basified with 1 N NaOH (50 mL). The aqueous layer was extracted with ether (2 x 300 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude oil was purified with

Example 326B

tert-butyl 1-(4-aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ylcarbamate

The nitro group of Example 326A was reduced with by the iron reduction procedure described previously.

MS (DCI/NH_3) m/e 343 $(M + H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.16 (s, 1H), 7.10 (d, 2H), 6.69 (s, 1H), 6.64 (d, 2H), 1.33 (s, 9H).

Example 326C

tert-butyl 1-{4-[(2-fluorobenzoyl)amino]phenyl}-3-(trifluoromethyl)-1*H*-pyrazol-5-ylcarbamate

Example 326B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

MS (DCI/NH_3) m/e 465 $(M + H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.66 (s, 1H), 9.43 (s, 1H), 8.10 (dt, 1H), 7.89 (d, 2H), 7.70 (dt, 1H), 7.51 (d, 2H), 7.50-7.29 (m, 2H), 6.79 (s, 1H), 1.34 (s, 9H).

Example 326

2-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide

To an ice cold (0 °C) flask containing Example 326C (25 mg, 0.054 mmol) was added sulfuric acid (1 mL). This mixture was stirred at room temperature for 30 min. 30% Hydrogen peroxide (0.5 mL) solution was then added and the resulting mixture was stirred at room temperature for 20 hours. The mixture was poured into saturated sodium bicarbonate solution (30 mL), and the aqueous layer was extracted with ethyl acetate (3 x 30 mL) The combined organic layers was dried over sodium sulfate, filtered and concentrated. The crude oil was purified by flash column chromatography with 10% ethyl acetate/90% hexane to afford the title compound as an oil (7 mg, 33% yield).

MS (DCI/NH_3) m/e 412 $(M + NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.76 (s, 1H), 8.15 (s, 1H), 7.91 (d, 2H), 7.75-7.58 (m, 3H), 7.67 (d, 2H), 7.43- 7.27 (m, 2H).

Example 327

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.45 (s, 1H), 8.89 (d, 1H), 8.59 (d, 1H), 8.57-8.52 (m, 1H), 8.16 (d, 2H), 8.08 (s, 1H), 7.78 (dt, 1H), 7.21 (d, 2H).

Example 329B

N-(4-nitrophenyl)-3-pyridinecarbohydrazonoyl chloride

To a solution of the Example 329A (6 g, 0.025 mol) in DMF (10 mL) at 0 °C was added a solution of N-chlorosuccinimide (3.45 g, 0.026 mol, 1.05 eq) in N, N-dimethylformamide (15 mL) dropwise over 30 minutes. After addition, the resulting dark green mixture was stirred at room temperature for two hours. Then it was poured into ice water with stirring. The resulting light brown solid was filtered, and dried in a vacuum oven at 40 °C for 12 hours to give the title compound (4.9 g, 71% yield) as an orange solid which was used in the next step without additional purification.

MS (DCI/NH_3) m/e 277 $(M+1)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.91 (s, 1H), 9.17 (d, 1H), 8.68 (dd, 1H), 8.32 (dd, 1H), 8.20 (d, 2H), 7.61-7.53 (m, 3H).

Example 329C

methyl 1-(4-nitrophenyl)-3-(3-pyridinyl)-1*H*-pyrazole-5-carboxylate

Example 329B (2.0 g, 7.2 mmol), methyl α–chloroacrylate (1.5 g, 10.8 mmol, 1.5 eq), toluene (15 mL), and triethylamine (2.5 mL,18 mmol, 2.5 eq) were combined and heated at 80°C for 8 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 mL), and washed with 1N HCl (30 mL), and saturated NaCl solution (30 mL). The organic portion was dried over Na_2SO_4, filtered, and concentrated in vacuo. This dark brown crude oil was purified by flash chromatography, using ethyl acetate-hexane (v/v, 3:7) to give the pyrazole (650 mg, 28%) as a brown oil.

MS (DCI/NH_3) m/e 243 $(M+1)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.19 (d, 1H), 8.60 (dd, 1 H), 8.39 (d, 2H), 8.33 (dd, 1H), 7.94 (d, 2H), 7.88 (s, 1H), 7.50 (dd, 1H).

Example 329D

[1-(4-nitrophenyl)-3-(3-pyridinyl)-1*H*-pyrazol-5-yl]methanol

To a -78 °C solution of Example 329C (650 mg, 2.0 mmol) in THF (30 mL) was added DIBAL (1M soln in hexane, 6.7 mL, 6.7 mmol) dropwise with stirring. After two hours at -78

Example 329G

3-[5-(difluoromethyl)-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl]pyridine

To a cold (0 °C) solution of 1,3-dibromo-5,5-dimethylhydantoin (302 mg, 1.06 mmol) in anhydrous dichloromethane (5 mL) under argon atmosphere was added HF-pyridine (0.2 mL, 0.88 mmol), followed by Example 329F (130 mg, 0.35 mmol). The resulting red solution was stirred at 0 °C for 45 minutes, then diluted with dichloromethane (10 mL) and quenched with $NaHCO_3$ solution (10 mL). The organic layer was separated and washed with more $NaHCO_3$ solution (10 mL) dried with Na_2SO_4, filtered and concentrated in vacuo to give 100 mg of black crude material. This crude product was purified by HPLC with ethyl acetate-hexane (v/v, 6:4) to give the difluoromethane (40 mg, 46%) as an oil.

See Reference: Katzenellenbogen, J.A.; Sondej, S.C. *J. Org. Chem.* **1986**, *51(18)*, 3508-3513.

MS (DCI/NH_3) m/e 317 $(M+1)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.19 (d, 1H), 8.62 (dd, 1H), 8.46 (d, 2H), 8.33 (dt, 1H), 7.96 (d, 2H), 7.65 (s, 1H), 7.52 (dd, 1H), 7.49 (s, 1H).

Example 329H

4-[5-(difluoromethyl)-3-(3-pyridinyl)-1*H*-pyrazol-1-yl]aniline

The title compound was prepared by iron powder and ammonium chloride reduction as previously described. The product was used in the subsequent step without additional purification or charactherization.

Example 329

N-(4-(5-(difluoromethyl)-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 329H was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 176-178 °C;

MS (ESI-) m/e 408 $(M-1)^-$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.14 (d, 1H), 8.8 (d, 1H), 8.64-8.58 (m, 2H), 8.48 (dd, 1H), 8.29 (dt, 1H), 7.92 (d, 2H), 7.75 (t, 1H), 7.65 (d, 2H), 7.53-7.46 (m, 2H), 3.72 (t, 1H).

Example 330

N-(4-(5-cyano-3-(2-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

carboxamide

Example 331A

1-(4-nitrophenyl)-3-(3-pyridinyl)-1*H*-pyrazole-5-carbonitrile

The title compound was prepared in 32% yield using the methodology described in the preparation of Example 304 using 2-chloroacrylonitrile and the chlorohydrazone previously described in the preparation of Example 329.

MS (DCI) m/e 292 $(M+1)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.19-9.16 (m, 1H), 8.66 (d, 1H), 8.51 (d, 2H), 8.37-8.30 (m, 1H), 8.23 (s, 1H), 8.17 (d, 2H), 7.56 (dd, 1H).

Example 331B

1-(4-aminophenyl)-3-(3-pyridinyl)-1*H*-pyrazole-5-carbonitrile

The title compound was prepared in 84% yield from the 331A using methodology described in the preparation of Example 304.

MS (DCI) m/e 262 $(M+1)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.10 (d, 1H), 8.25 (dt, 1H), 7.95 (s, 1H), 7.50 (dd, 1H), 7.39 (d, 2H), 6.70 (d, 2H), 5.65 (s, 2H).

Example 331

N-(4-(5-cyano-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example 331B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 215-218 °C;

MS (ESI) m/e 386 $(M-1)^-$, 388 $(M+1)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.15 (d, 1H), 8.63 (dd, 1H), 8.30 (dt, 1H), 8.10 (s, 1H), 7.95 (d, 2H), 7.85 (d, 2H), 7.54 (dd, 1H), 2.80 (s, 3H).

Example 332

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 332A

5-bromo-1-(4-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole

Example 326B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
MS (DCI/NH_3) m/e 483 $(M + NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.95 (s, 1H), 9.46 (s, 1H), 8.79 (s, 1H), 8.62 (d, 1H), 7.87 (d, 2H), 7.74 (t, 1H), 7.54 (d, 2H), 6.80 (s, 1H), 1.33 (s, 9H).

Example 333

3-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

A solution of Example 333A (100 mg, 0.215 mmol) in trifluoroacetic acid (2 mL) and methylene chloride (2 mL) was stirred at room temperature for 30 min. The solvent was removed in vacuo and the residue was dissolved in acetonitrile (1 mL). Sodium nitrate (300 mg) and copper sulfate were mixed together in a separate flask with acetonitrile (2 mL) and water (1 mL). The amine solution was added slowly over 5 minutes, then the resulting mixture was allowed to stir for 15 minutes. The reaction mixture was poured into saturated sodium bicarbonate solution (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography with 50% ethyl acetate/ 50% hexane to obtain the title compound (8 mg, 9% yield).
mp 188-190 °C;
MS (DCI/NH_3) m/e 413 $(M + NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.01 (s, 1H), 8.80 (s, 1H), 8.63 (d, 1H), 8.14 (s, 1H), 7.89 (d, 2H), 7.76 (t, 1H), 7.69 (d, 2H);
Anal. calcd for $C_{16}H_9F_4N_5O_3$: C, 48.61; H, 2.29; N, 17.71. Found: C, 48.89; H, 2.37; N, 17.38.

Example 334

3-fluoro-*N*-{4-[5-nitro-3-(3-pyridinyl)-1*H*-pyrazol-1-yl]phenyl}isonicotinamide

Example 334A

1-(4-nitrophenyl)-3-(3-pyridinyl)-1*H*-pyrazol-5-amine

3-Oxo-3-pyridin-3-yl-propionitrile (3.57g, 24.4 mmol)[Chem. Abstr.; 60; 10689d; 1964] and p-nitrophenylhydrazine (3.74g, 24.4 mmol) were dissolved in ethanol (100 mL), treated with 4N HCl in dioxane (61 mL) and refluxed for 2 hours. After cooling to ambient temperature and evaporation to dryness, the residue was partitioned between ethyl acetate and

7.06 (dm, J=9Hz, 0.67H), 7.04 (s, 0.33H), 6.82 (s, 0.67H), 6.67-6.62 (m, 2H), 5.43 (s, 0.67H), 5.36 (s, 1.33H), 1.30-1.38 (m, 12H).

Example 334D

N-[4-[3-(3-pyridyl)-5-(bis-Boc-amino)-1H-pyrazol-1-yl]phenyl]-3-fluoropyridin-4-yl-carboxamide

Example 334C was processed as in Example (i)-a (Method 5, 6, or 7) to provide 530 mg of product as a mixture of mono and bis Boc protected substances.

MS (ESI-) m/e 473(M-H)$^-$;

^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 9.23 (s, 0.4H), 9.09 (d, J=2Hz, 0.6H), 9.06 (d, J=2Hz, 0.4H), 8.78 (s, 1H), 8.62 (d, J=5Hz, 1H), 8.58-8.54 (m, 1H), 8.26-8.20 (m, 1H), 7.92-7.84 (m, 2H), 7.76-7.73 (m, 1H), 7.59 (dm, J=9Hz, 0.8H), 7.52-7.44 (m, 2.2H), 7.18 (s, 0.6H), 6.93 (s, 0.4H), 5.98 (s, 0.4H);

Example 334E

N-[4-[3-(3-pyridyl)-5-amino-1H-pyrazol-1-yl]phenyl]-3-fluoropyridin-4-yl-carboxamide

Example 334E (530 mg) was treated with 4N HCl in dioxane (20 mL) for 1 hour. The excess reagent and solvent were removed by evaporation in vacuo, and the residue (0.60 g) was used without purification.

MS (ESI-) m/e 373(M-H)$^-$; 409(M+Cl)$^-$;

^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 10.92 (s, 1H), 9.15 (s, 1H), 8.79 (s, 1H), 8.72 (d, J=6Hz, 1H), 8.67-8.62 (m, 2H), 7.89-7.85 (m, 2H), 7.74 (t, J=5Hz, 1H), 7.66 (dm, J=9Hz, 2H), 6.14 (s, 1H);

Example 334

3-fluoro-*N*-{4-[5-nitro-3-(3-pyridinyl)-1*H*-pyrazol-1-yl]phenyl}isonicotinamide

Example 334E (54 mg, 0.14 mmol) in 10% H_2SO_4 (1 mL) was added dropwise to $NaNO_2$ (400 mg) in water (2 mL) at 50 °C. The outgassing of the reaction stopped after approximately 15 minutes. The reaction was cooled to ambient temperature and diluted with 1N $NaHCO_3$ solution. The product was extracted into ethyl acetate, the ethyl acetate layer was washed with water (2x) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by chromatography on silica gel (2g Alltech Extract-Clean™ silica) by elution with hexanes-ethyl acetate (1:2) to provide 17 mg (0.042 mmol, 30%) of the title compound as an off-white solid.

4-[5-chloro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

A solution of Example 336A (90 mg, 0.329 mmol) in acetonitrile (1 mL) was added to to a cold solution (0 °C) of copper chloride (66 mg, 0.49 mmol) and t-butyl nitrite (0.058 mL, 0.49 mmol) in acetonitrile (2 mL). The resulting mixture was stirred for 30 minutes, then poured into brine (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography with 10% ethyl acetate/ 90% hexane to afford the chlorotriazole as an oil (70 mg, 73% yield). MS (DCI/NH_3) m/e 280 $(M+NH_4,)^+$ (For aniline produced by the analysis.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.50 (d, 2H), 8.07 (d, 2 H). This nitro compound was subjected to the usual iron reduction conditions and used without purification in the next step. TLC analysis indicated that the reaction was complete.

Example 336

N-{4-[5-chloro-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl}-3-fluoroisonicotinamide

mp 167-170 °C;
MS (DCI/NH_3) m/e 386 $(M + H)^+$;
^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.08 (s, 1H), 8.80 (s, 1H), 8.63 (d, 1H), 7.95 (d, 2H), 7.76 (d, 2H), 7.75 (s, 1H).

N-(4-(5-chloro-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 325B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 167-170 °C;
MS (DCI/NH_3) m/e 386 $(M + H)^+$;
^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.08 (s, 1H), 8.80 (s, 1H), 8.63 (d, 1H), 7.95 (d, 2H), 7.76 (d, 2H), 7.75 (s, 1H).

Example 337

4-methyl-N-(4-(5-nitro-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-1,2,3-thiadiazole-5-

Example 337A

tert-butyl 1-(4-{[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]amino}phenyl)-3-(3-pyridinyl)-1*H*-pyrazol-5-ylcarbamate

^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.18 (d, 1H, J=2 Hz), 8.63 (dd, 1H, J=2,5 Hz), 8.33 (dt, 1H, J=8,2 Hz), 8.20 (s, 1H), 7.87 (d, 2H, J=9 Hz), 7.69 (d, 2H, J=9 Hz), 7.53 (dd, 1H, J=5,8 Hz), 2.86 (s, 3H).

Example 338

N-(4-(5-cyano-3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 338A

1,3-thiazole-2-carbaldehyde *N*-(4-nitrophenyl)hydrazone

The hydrazone was prepared from 4-nitrophenylhydrazine and 2-thiazolecarboxaldehyde in 88% yield using the methodology described in the preparation of Example 300A.

MS (DCI) m/e 249 $(M+1)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 1H), 8.09 (d, 2H), 7.88 (d, 1H), 7.69 (d, 1H), 7.09 (d, 2H).

Example 338B

N-(4-nitrophenyl)-1,3-thiazole-2-carbohydrazonoyl chloride

The chlorohydrazone was prepared in 88% yield from the hydrazone prepared above using methodology described in the preparation of Example 300B.

MS (DCI) m/e 283 $(M+1)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.10 (s, 1H), 8.24 (d, 2H), 7.96 (d, 1H), 7.92 (d, 1H), 7.48 (d, 2H).

Example 338C

1-(4-nitrophenyl)-3-(1,3-thiazol-2-yl)-1*H*-pyrazole-5-carbonitrile

The title compound was prepared in 15% yield using the chlorohydrazone prepared above and the reagents and methodology described in the preparation of Example 300C.

MS (DCI) m/e 298 $(M+1)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.51 (d, 2H), 8.15 (d, 2H), 8.09 (s, 1H), 8.04 (d, 1H), 7.97 (d, 1H).

Example 338D

1-(4-aminophenyl)-3-(1,3-thiazol-2-yl)-1*H*-pyrazole-5-carbonitrile

The compound was prepared in 36% yield from the nitrophenyl compound prepared above using the methodology described in the preparation of Example 300D.

MS (ESI) m/e 268 $(M+1)^+$, 266 $(M-1)^-$.

4-[3-(5-bromo-3-pyridinyl)-5-(difluoromethoxy)-1*H*-pyrazol-1-yl]phenylamine

This intermediate was prepared by reduction of the above compound with iron powder in 82% yield as described in the preparation of Example 322B.

MS (DCI/NH_3) m/e 400 $(M+NH_4)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 9.04 (d, 1H), 8.67 (d, 1H), 8.45 (t, 1H), 7.54-7.06 (t, 1H), 7.22 (d, 2H), 6.93 (s, 1H), 6.65 (d, 2H), 5.47 (s, 2H).

Example 339

N-(4-(3-(5-bromo-3-pyridinyl)-5-(difluoromethoxy)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 339C was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 179-180 °C;

MS (DCI/NH_3) m/e 506 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 10.94 (s, 1H), 9.1 (d, 1H), 8.8 (s, 1H), 8.72 (d, 1H), 8.62 (d, 1H), 8.51 (t, 1H), 7.9 (d, 2H), 7.74 (t, 1H), 7.71 (d, 2H), 7.13-7.61 (t, 1H), 7.05 (s, 1H).

Example 340

N-(4-(5-cyano-3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example 338D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 230°C;

MS (ESI-) m/e 392 $(M-1)^-$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.10 (d, 1H), 7.96 (d, 2H), 7.97 (s, 1H), 7.89 (d, 1H), 7.85 (d, 2H), 2.86 (d, 3H).

Example 341

N-(4-(5-cyano-3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 338D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 162-163 °C;

MS (DCI/NH_3) m/e 434 $(M+1)^+$;

2-[1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-1,3-thiazole

To a cooled (0 °C) slurry of sodium hydride (95%, 432 mg, 17 mmol) and dry DMF (20 mL) was added dropwise Example 342B (3.4 g, 16 mmol) in dry DMF (5 mL). The resulting mixture was stirred for 10 minutes, 4-fluoronitrobenzene (1.80 mL, 17 mmol) was also added dropwise to the reaction mixture at 0 °C. After addition, the mixture was heated to reflux for 3 hours. After the reaction was complete, the reaction mixture was cooled to room temperature, partitioned between 30 mL of ethyl acetate (30 mL) and water (20 mL). The organic layer was separated, dried with Na_2SO_4, filtered and concentrated in vacuo to give a mixture of regioisomers (5 g, 91%, 2:1 mixture of regioisomers). This crude material was not purified before next iron reduction step.

MS (ESI) m/e 341 $(M+1)^+$;

Compound 1:1H NMR (DMSO-d_6, 300 MHz) δ 8.36 (d, 2H), 7.97 (d, 1H), 7.91 (d, 1H), 7.82 (d, 2H), 7.66 (s, 1H);

Compound 2: 1H NMR (DMSO-d_6, 300 MHz) δ 8.47 (d, 2H), 8.02 (d, 1H), 7.95 (d, 2H), 7.89 (d, 1H), 7.73 (s, 1H).

Example 342D

4-[3-(1,3-thiazol-2-yl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]aniline

Iron powder (5.75 g, 103 mmol), ammonium chloride(595 mg, 12 mmol), Example 342C (isomeric mixture from previous step, 5g, 15 mmol) and ethanol-H_2O (4:1, 50 mL) were combined. This resulting black mixture was heated to reflux for 8 hours. The reaction mixture was cooled to room temperature, passed through a diatomaceous earth pad and a silica gel plug, eluting with ethyl alcohol. After the desired fractions was combined and concentrated in vacuo, the residue was diluted with dichloromethane (20 mL) and washed with $NaHCO_3$ (20 mL X 2). The organic portion was dried with Na_2SO_4, filtered and concentrated in vacuo. This brown crude product was purified by flash chromatography, eluting with ethyl acetate-hexanes (v/v, 2:8) to give the desired product as a pale white solid (1.5 g, 33% yield).

MS (ESI) m/e 311 $(M+1)^+$, 309 $(M-1)^-$;

^1H NMR (DMSO-d_6, 300 MHz) δ 7.97 (d, 1H), 7.82 (d, 1H), 7.49 (s, 1H), 7.19 (d, 2H), 6.65 (d, 2H), 5.65 (s, 2H).

Example 342

mp 194-195 °C;
MS (DCI/NH_3) m/e 462 $(M + H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.01 (s, 1H), 8.80 (s, 1H), 8.62 (d, 1H), 7.91 (d, 2H), 7.75 (t, 1H), 7.60 (d, 2H), 7.41 (s, 1H), 2.63 (s, 3H), 2.51 (s, 3H).

Example 344

3-fluoro-N-(4-(5-(1-methyl-1H-pyrrol-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 344A

4-[5-(1-methyl-1*H*-pyrrol-3-yl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenylamine

3-Acetyl-1-methyl pyrrole (5 g, 40.65 mmol), sodium methoxide (2.6 g, 48.15 mmol) and methyl trifluoroacetate (4.9 mL, 48.15 mmol) were combined with diethyl ether (200 mL). The mixture was heated to reflux for 2 hours. After cooling to room temperature, solvent was removed. Hydrazine monohydrate (2.16 mL, 44.58 mmol) and toluene (150 mL) were added, and the reaction mixture was heated to reflux for 16 hours. Upon cooling to room temperature, solvent was once again removed. The crude material was dissolved in dimethylformamide (100 mL) and cooled to 0 °C. This solution was added dropwise to a mixture of sodium hydride (60% in mineral oil, 1.79g, 44.72 mmol) in dimethylformamide (30 mL). After stirring at 0 °C for 30 minutes, 1-fluoro-4-nitrobenzene (4.3 mL, 40.65 mmol) was added. The resulting mixture was warmed to 90 °C for 16 hours. After cooling to 0 °C, the reaction was quenched with water (5 mL). The quenched mixture was partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous layer was back extracted with ethyl acetate (2 x 100 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over magnesium sulfate and concentrated to dryness. Iron powder (15.6 g, 0.28 mol), ammonium chloride (2.26 g, 40.65 mmol) and a mixture of ethanol/water (200 mL, 3:1/v:v) were added to the crude intermediate. The mixture was heated to reflux for 1 hour. After cooling to ambient temperature, the reaction mixture was passed through a pad of diatomaceous earth (20 g). The filtrate was concentrated to dryness. The crude product was purified by silica gel chromatography eluting with 40% acetone in hexanes (v:v). Fractions containing the desired product were combined and freed of solvent (2.11 g, 17 % yield).
MS (DCI/NH_3) m/e 307 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.01 (d, 2H), 7.95 (s, 1H), 6.72 (t, 1H), 6.60 (d, 2H), 6.37 (t, 1H), 5.85 (m, 1H), 5.53 (s, 2H), 3.53 (s, 3H)

and 10 g anhydrous magnesium sulfate), and the product eluted with 50% acetone in hexanes (v:v). Fractions containing the desired product and the regioisomer were combined and concentrated in vacuo. The two isomers were separated by HPLC (silica gel, YMC) eluting with 10% ethyl acetate in hexanes. The regioisomers were present in a 1:2 ratio with the desired material being the minor constituent. Overall yield: 0.35 g (26%) of the desired product.

MS (DCI/NH_3) m/e 324 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.45 (d, 2H), 7.92 (d, 2H), 7.83 (m, 1H), 7.62 (s, 1H), 7.05 (m, 1H), 6.67 (m, 1H).

Example 345C

(±) 4-[3-tetrahydro-2-furanyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenylamine

A solution of the above compound and 10% palladium on carbon in methanol containgin one drop of concentrated hydrochloric acid was hydrogenated at 4 atm at room temperature for 18 hours, filtered through a short silica gel plug, and concentrated to provide the desire compound.

MS (DCI/NH_3) m/e 298 $(M+H)^+$.

Example 345D

3-fluoro-N-(4-(3-tetrahydro-2-furanyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 345C was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 116-118 °C;

MS (DCI/NH_3) m/e 421 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 11.00 (s, 1H), 8.80 (d, 1H), 8.62 (dd, 1H), 7.9 (d, 2H), 7.85 (t, 1H), 7.52 (d, 2H), 7.10 (s, 1H), 4.95-4.90 (m, 1H), 3.97-3.89 (m, 1H), 3.81-3.73 (m, 1H), 2.30-2.21 (m, 1H), 2.27-1.90 (m, 3H).

Example 346

3-chloro-N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide

Example 325B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound using 3-chloroisonicotinic acid prepared as described in the reference below.

Reference: Lecomte, L.; Ndzi, B.; Queguiner, G.; Turck, A. FR. 2,686,340-A1.

mp 184-185 °C;

^{1}H NMR (DMSO-d_6, 300 MHz) d 8.40 (d, 2H), 8.17 (d, 2H), 7.92 (d, 1H), 7.79 (d, 1H), 6.10 (s, 1H).

Example 347C

2-[5-chloro-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl]-1,3-thiazole

A mixture of the Example 347B (938 mg, 3.25 mmol) and phenylphosphinic dichloride (5.0 mL, 35.3 mmol) was heated at 150 °C for 24 hours. The reaction mixture was cooled and poured slowly into saturated sodium bicarbonate solution (150 mL). The aqueous layer was extracted with ether (3 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash chromatography with 90% hexane/ 10% ethyl acetate affording the title compound as a yellow oil (215 mg, 22% yield).

MS (DCI/NH_3) m/e 307 $(M + H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.46 (d, 2H), 8.04 (d, 2H), 7.99 (d, 1H), 7.86 (d, 1H), 7.29 (s, 1H).

Example 347D

4-[5-chloro-3-(1,3-thiazol-2-yl)-1*H*-pyrazol-1-yl]phenylamine

The nitro group of Example 347C was reduced with iron as described previously.

MS (DCI/NH_3) m/e 277 $(M + H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.92 (d, 1H), 7.78 (d, 1H), 7.21 (d, 2H), 7.06 (s, 1H), 6.68 (d, 2H), 5.58 (s, 2H).

Example 347

N-(4-(5-chloro-3-(1,3-thiazol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 347D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 194-195 °C;

MS (DCI/NH_3) m/e 400 $(M + H)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.98 (s, 1H), 8.79 (s, 1H), 8.63 (d, 1H), 7.95 (d, 1H), 7.93 (d, 2H), 7.81 (d, 1H), 7.75 (t, 1H), 7.68 (d, 2H), 7.17 (s, 1H);

Anal. calcd for $C_{18}H_{11}ClFN_5OS$: C, 54.07; H, 2.77; N, 17.51. Found: C, 53.90; H, 3.05; N, 17.00.

mp 221-222 °C;
MS (ESI-) m/e 374 $(M-1)^-$;
^1H NMR (DMSO-d_6, 300 MHz) δ 11.06 (s, 1H), 8.8 (d, 1H), 8.63 (dd, 1H), 8.08 (s, 1H), 7.97 (d, 2H), 7.82 (d, 2H), 7.76 (t, 1H);
IR (KBr) cm^{-1} 3188, 3132, 3046, 2244, 1694, 1609, 1557, 1513, 1475, 1417, 1326, 1242, 1153, 1129, 1101, 972, 843.

Example 352

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide

Example 322B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 130-131 °C;
MS (DCI/NH_3) m/e 433 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.7 (s, 1H), 7.92 (d, 2H), 7.7 (t, 1H), 7.61 (d, 2H), 7.6 (m, 1H), 7.32-7.41 (m, 2H), 7.15-7.65 (t, 1H), 6.82 (s, 1H).

Example 353

2-chloro-N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide

Example 322B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 122-123 °C;
MS (DCI/NH_3) m/e 449 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.82 (s, 1H), 7.92 (d, 2H), 7.62 (d, 2H), 7.59-7.66 (m, 2H), 7.45-7.57 (m, 2H), 7.16-7.64 (t, 1H), 6.85 (s, 1H).

Example 354

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2,3-difluorobenzamide

Example 322B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 154-155 °C;
MS (DCI/NH_3) m/e 451 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.69 (s, 1H), 7.79 (d, 2H), 7.53 (d, 3H), 7.4 (t, 1H), 7.2 (m, 1H), 7.09-7.45 (t, 1H), 6.69 (s, 1H).

MS (DCI/NH_3) m/e 260 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.15 (d, 2H), 6.81 (s, 1H), 6.65 (d, 2H), 5.50 (s, 2H).

Example 355

N-(4-(5-chloro-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide

Example 355B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 150-152 °C;
MS (DCI/NH_3) m/e 386 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 8.17 (m, 1H), 7.89 (d, 2H), 7.76 (t, 1H), 7.62 (d, 2H), 6.96 (s, 1H), 6.86 (m, 1H), 2.84 (s, 3H).

Example 356

N-(4-(5-chloro-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 355B was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 165-166 °C;
MS (DCI/NH_3) m/e 383 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.98 (s, 1H), 8.80 (s, 1H), 8.63 (d, 1H), 8.18 (s, 1H), 7.90 (d, 2H), 7.77-7.74 (m, 2H), 7.65 (d, 2H), 6.97 (s, 1H), 6.87 (m, 1H).

Example 357

N-(4-(5-cyano-3-tetrahydro-2-furanyl-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 357A

(±)-N'-(4-nitrophenyl)tetrahydro-2-furancarbohydrazide

A mixture of 4-nitrophenylhydrazine (719 mg, 4.70 mmol), tetrahydro-2-furoic acid (818 mg, 7.05 mmol), dimethylaminopyridine (860 mg, 7.05 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.34 g, 7.05 mmol) in methylene chloride (20 mL) was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and the organic mixture was washed with 1N HCl solution (150 mL) and saturated sodium bicarbonate solution (150 mL). The organic layer was dried

Example 357

N-(4-(5-cyano-3-tetrahydro-2-furanyl-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 357D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 160-162 °C;

MS (DCI/NH_3) m/e 395 $(M + NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.01 (s, 1H), 8.80 (s, 1H), 8.62 (d, 1H), 7.93 (d , 2H), 7.75 (t, 1H), 7.74 (d, 2H), 7.43 (s, 1H), 4.96 (t, 1H), 3.93 (m, 1H), 3.80 (m, 1H), 2.30 (m, 1H), 1.99 (m, 3H).

Example 358

N-(4-(5-(difluoromethoxy)-3-(1-methyl-1H-pyrrol-3-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 358A

methyl 3-(1-methyl-1*H*-pyrrol-3-yl)-3-oxopropanoate

To a -78° C solution of lithium hexamethyldisilazide (2 mL, 2 mmol) in tetrahydrofuran (5 mL) was added 3-acetyl-1-methylpyrrole (0.24 mL, 2 mmol). The reaction was warmed to 0 °C and stirred for 1 hour. The reaction mixture was again cooled to -78 °C, and methylcyanoformate (0.19 mL, 2.4 mmol) was added. After stirring for 1 hour at -78 °C, the reaction was slowly allowed to warm to room temperature. Then the reaction mixture was partitioned between ether and 1 N HCl. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give crude material. Purification by HPLC (silica gel; acetone-hexane, 20:80) provided the desired product (0.18 g, 50% yield).

MS (DCI/NH_3) m/e 199 $(M+NH_4)^+$;

^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.64 (t, 1H), 6.84 (dd, 1H), 6.47 (dd, 1H), 5.45 (s, 1H), 3.67 (s, 3H), 3.66 (s, 3H).

Example 358B

3-(1-methyl-1*H*-pyrrol-3-yl)-1-(4-nitrophenyl)-1*H*-pyrazol-5-ol

Condensation of of the β-ketoester prepared above with p-nitrophenylhydrazine using conditions previously described furnished the hydroxypyrazole in 64% yield.

MS (DCI/NH_3) m/e 302 $(M+NH_4)^+$;

Example 355A (1 g, 3.89 mmol) and K_2CO_3 (1.53 g, 11.1 mmol) were combined in dimethylformamide (10 mL) and heated to 50 °C. Chlorodifluoromethane was bubbled into the reaction mixture for 45 minutes. The mixture was then cooled to room temperature and partition between saturated NaCl solution (50 mL) and diethyl ether (50 mL). The organic layer was separated, the aqueous layer was washed again with diethyl ether (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was passed through a silica gel cake (150 mL) eluting with 20% acetone in hexanes and then concentrated in vacuo to provide the desired product.

MS (DCI/NH_3) m/e 292 $(M+H)^+$ (For the aniline produced under the analysis conditions.);

^1H NMR (DMSO-d_6, 300 MHz) δ 8.42 (d, 2H), 8.29 (s, 1H), 7.99 (d, 2H), 7.80 (t, 1H), 7.42 (t, 1H), 6.92 (s, 1H), 6.70 (s, 1H).

The crude product was redissolved in 20 mL of ethanol/water (3:1/v:v). Iron powder (1.5g, 27.27 mmol) and ammonium chloride (0.206 g, 3.89 mmol) were added and the mixture was warmed to reflux for 1 hour. Upon cooling to room temperature, solvent was removed in vacuo, and the residue was loaded onto a filter cake (100 mL silica gel and 15 g anhydrous magnesium sulfate) and then eluted with 50% acetone in hexanes (v:v). Fractions containing the desired product were combined and solvent removed in vacuo leaving the product as an off white solid (0.52 g, 48% overall yield).

MS (DCI/NH_3) m/e 292 $(M+H)^+$.

Example 359

N-(4-(5-(difluoromethoxy)-3-(3-furyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 359A was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.

mp 172-174 °C;

MS (DCI/NH_3) m/e 415 $(M+H)^+$;

^1H NMR (DMSO-d_6, 300 MHz) δ 8.77 (m, 1H), 8.60 (m, 1H), 8.20 (m, 1H), 7.87 (d, 2H), 7.75 (m, 1H), 7.73 (m, 1H), 7.63 (d, 2H), 7.35 (t, 1H), 6.89 (m, 1H), 6.55 (s, 1H).

Example 360

N-(4-(5-(difluoromethoxy)-3-(1-methyl-1H-pyrrol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 360A

The aniline was prepared using the iron powder reduction conditions described in the preparation of 322B in quantitative yield.
MS (DCI/NH_3) m/e 305 $(M+H)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 7.66-7.18 (t, 1H), 7.2 (d, 2H), 6.8 (t, 1H), 6.64 (d, 2H), 6.4 (dd, 1H), 6.36 (s, 1H), 6.03 (dd, 1H), 5.39 (s, 2H), 3.87 (s, 3H).

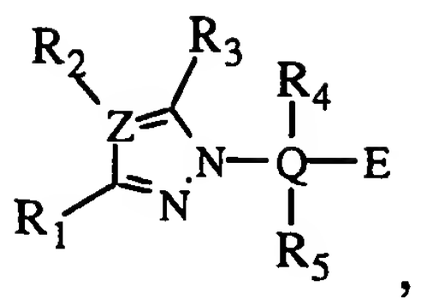
Example 360

N-(4-(5-(difluoromethoxy)-3-(1-methyl-1H-pyrrol-2-yl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide

Example 360D was processed as in Example (i)-a (Method 5, 6, or 7) to provide the title compound.
mp 154-155 °C;
MS (DCI/NH_3) m/e 428 $(M+NH_4)^+$;
^1H NMR (DMSO-d_6, 300 MHz) δ 10.9 (s, 1H), 8.8 (s, 1H), 8.62 (d, 1H), 7.87 (d, 2H), 7.74 (t, 1H), 7.68 (d, 2H), 7.14-7.62 (t, 1H), 6.84 (t, 1H), 6.06 (t, 1H), 4.49 (s, 1H), 4.48 (t, 1H), 3.92 (s, 3H).

WHAT IS CLAIMED IS:

1. A compound having Formula **I**



,

I

or a pharmaceutically acceptable salt or prodrug thereof, where

R_1 and R_3 are independently selected from

(1) hydrogen,

(2) aryl,

(3) perfluoroalkyl of one to fifteen carbons,

(4) halo,

(5) -CN,

(6) $-NO_2$,

(7) -OH,

(8) -OG where G is a hydroxyl protecting group,

(9) $-CO_2R_6$ where R_6 is selected from

(a) hydrogen,

(b) cycloalkyl of three to twelve carbons,

(c) aryl,

(d) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkyl of one to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) thioalkoxy of one to fifteen carbons,

(iv) halo,

(v) $-NO_2$, and

(vi) $-N_3$,

(e) a carboxy protecting group,

(f) alkyl of one to fifteen carbons,

(g) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4

(f) aryl,

(g) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkyl of one to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) thioalkoxy of one to fifteen carbons,

(iv) halo,

(v) $-NO_2$, and

(vi) $-N_3$,

(h) $-OR_6$,

provided that only one of R_7 or R_8 is $-OR_6$,

(i) a nitrogen protecting group,

(j) alkyl of one to fifteen carbons,

(k) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkoxy of one to fifteen carbons,

(ii) thioalkoxy of one to fifteen carbons,

(iii) aryl,

(iv) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(v) cycloalkyl of three to fifteen carbons,

(vi) halo,

(vii) $-CO_2R_6$, and

(viii) -OH,

(l) alkenyl of three to fifteen carbons,

provided that a carbon of a carbon-carbon double bond is not attached directly to nitrogen,

(m) alkynyl of three to fifteen carbons,

(f) alkenyl of two to fifteen carbons, and

(e) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkenyl of two to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) -CN,

(iv) $-CO_2R_6$,

(v) -OH,

provided that no two -OH groups are attached to the same carbon,

(vi) thioalkoxy of one to fifteen carbons,

(vii) alkynyl of two to fifteen carbons,

(viii) aryl,

(ix) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(x) cycloalkyl of three to twelve carbons, and

(xi) halo,

(xii) $-NR_7R_8$,

(xiii) heterocycle, and

(xiv) heterocycle substituted with 1, 2, or 3, or 4 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(12) alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 halo substituents,

(20) $-NR_XC(=NR_{X'})NR_YR_Z$ where R_X, R_Y and R_Z are defined previously and $R_{X'}$ is selected from

(a) hydrogen and

(b) alkyl of one to fifteen carbons,

(21) $-NR_XC(O)OR_W$, where R_W is selected from

(a) alkyl of one to fifteen carbons and

(b) alkenyl of three to fifteen carbons,

provided that a carbon of a carbon-carbon double bond is not attached directly to oxygen, and

(22) $-OC(O)NR_7R_8$;

Z is nitrogen or carbon;

R_2 is absent or is selected from

(1) hydrogen,

(2) $-CO_2R_6$,

(3) alkyl of one to fifteen carbons,

(4) $-C(O)R_{6'}$ where $R_{6'}$ is selected from

(a) alkyl of one to fifteen carbons,

(b) aryl, and

(c) heterocycle,

(5) $-C(O)NR_{7'}R_{8'}$ where $R_{7'}$ and $R_{8'}$ are independently selected from

(a) hydrogen,

(b) alkyl of one to fifteen carbons, or

$R_{7'}$ and $R_{8'}$ together with the nitrogen to which they are attached form a ring selected from

(i) piperidine,

(ii) piperazine,

(iii) morpholine,

(iv) thiomorpholine, and

(v) thiomorpholine sulfone

(6) perfluoroalkyl of one to fifteen carbons,

(7) cycloalkyl of three to ten carbons,

(8) alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents

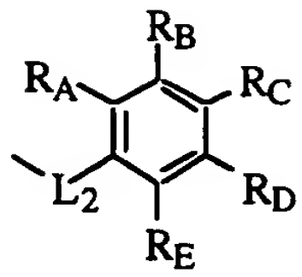
(a) hydrogen,
(b) cycloalkyl of three to twelve carbons,
(c) aryl,
(d) alkyl of one to fifteen carbons, and
(e) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from
(i) alkenyl of two to fifteen carbons,
(ii) alkoxy of one to fifteen carbons,
(iii) thioalkoxy of one to fifteen carbons,
(iv) alkynyl of two to fifteen carbons, and
(v) aryl,

(15) $-L_2$-heterocycle, and

(16) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3, or 4 substituents independently selected from
(a) alkyl of one to fifteen carbons,
(b) perfluoroalkyl of one to fifteen carbons,
(c) alkoxy of one to fifteen carbons,
(d) thioalkoxy of one to fifteen carbons,
(e) halo,
(f) $-N_3$, and
(g) $-NO_2$;

E is

(1) $-L_3$-B where L_3 is selected from
(a) a covalent bond,
(b) alkenylene of two to six carbons in the Z or E configuration,
(c) alkynylene of two to six carbons,
(d) $-C(X)-$,
(e) $-N=N-$,
(f) $-NR_7-$,
(g) $-N(R_7)C(O)N(R_8)-$,
(h) $-N(R_7)SO_2N(R_8)-$,
(i) $-X-$,
(j) $-(CH_2)_mO-$,

(i)  where L_2 is defined previously and R_A, R_B, R_C, R_D, and R_E are independently selected from

hydrogen,

alkanoyl where the alkyl part is one to fifteen carbons,

alkanoyloxy where the alkyl part is one to fifteen carbons,

alkoxy of one to fifteen carbons,

thioalkoxy of one to fifteen carbons,

alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo ,

perfluoroalkyl of one to fifteen carbons,

perfluoroalkoxy of one to fifteen carbons,

$-N_3$,

$-NO_2$,

-CN,

-OH,

-OG,

cycloalkyl of three to fifteen carbons,

halo,

$-CO_2R_6$

$-L_1NR_7R_8$

$-L_2R_9$

alkyl of one to fifteen carbons,

alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(=X),

alkanoyloxy where the alkyl part is one to fifteen carbons,

alkoxy of one to fifteen carbons,

substituents selected from the group consisting of halo,

(vi) thioalkoxy of one to fifteen carbons,

(vii) perfluoroalkoxy of one to fifteen carbons,

(viii) $-N_3$,

(ix) $-NO_2$,

(x) -CN,

(xi) -OH,

provided that no two -OH groups are attached to the same carbon,

(xii) -OG,

(xiii) cycloalkyl of three to fifteen carbons,

(xiv) halo,

(xv) $-CO_2R_6$,

(xvi) $-L_1NR_7R_8$,

(xvii) perfluoroalkyl of one to fifteen carbons,

(xviii) $-L_2$-heterocycle, and

(xix) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3, or 4 substituents independently selected from

(=X),

alkanoyl where the alkyl part is one to fifteen carbons,

alkanoyloxy where the alkyl part is one to fifteen carbons,

alkoxy of one to fifteen carbons,

alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo ,

thioalkoxy of one to fifteen carbons,

perfluoroalkyl of one to fifteen carbons,

perfluoroalkoxy of one to fifteen carbons,

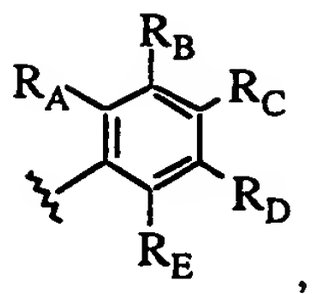
$-N_3$,

$-NO_2$,

-CN,

-OH,

provided that no two -OH groups are attached to the

(f)  ,

provided that when R_1 and R_3 are both perfluoroalkyl of one carbon, Z is carbon, R_2 is hydrogen, Q is phenyl that is 4-substituted by E relative to the position of attachment of the pyrazole ring to the phenyl group, R_4 and R_5 are hydrogen, E is $-L_3-B$, L_3 is $-N(R_7)C(X)-$, R_7 is hydrogen, X is oxygen, and R_A, R_B, R_D, and R_E are hydrogen, R_C is other than chloro, and

(g) heterocycle where the heterocycle can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(i) (=X),

(ii) alkanoyl where the alkyl part is one to fifteen carbons,

(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,

(iv) alkoxy of one to fifteen carbons,

(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(vi) halo ,

(vii) thioalkoxy of one to fifteen carbons,

(viii) perfluoroalkyl of one to fifteen carbons,

(ix) perfluoroalkoxy of one to fifteen carbons,

(x) $-N_3$,

(xi) $-NO_2$,

(xii) -CN,

(xiii) -OH,

provided that no two -OH groups are attached to the same carbon,

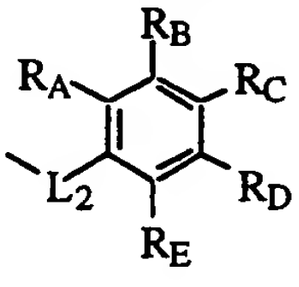
(xiv) -OG,

(xv) cycloalkyl of three to fifteen carbons,

(xvi) halo,

the C(=O) group

where (b), (c), and (d) can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(i) 

(ii) (=X),

(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,

(iv) alkoxy of one to fifteen carbons,

(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(vi) thioalkoxy of one to fifteen carbons,

(vii) perfluoroalkoxy of one to fifteen carbons,

(viii) $-N_3$,

(ix) $-NO_2$,

(x) -CN,

(xi) -OH,

provided that no two -OH groups are attached to the same carbon,

(xii) -OG,

(xiii) cycloalkyl of three to fifteen carbons,

(xiv) halo,

(xv) $-CO_2R_6$,

(xvi) $-L_1NR_7R_8$,

(xvii) perfluoroalkyl of one to fifteen carbons,

(xviii) $-L_2$-heterocycle, and

(xix) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3,or 4 substituents independently selected from

(=X),

alkanoyl where the alkyl part is one to fifteen carbons,

alkanoyloxy where the alkyl part is one to fifteen carbons,

alkoxy of one to fifteen carbons,

alkoxy of one to fifteen carbons substituted with 1, 2, 3,

alkyl of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(g) heterocycle, and

(h) heterocycle substituted with 1, 2, 3, or 4 substituents independently selected from

(i) (=X),

(ii) alkanoyl where the alkyl part is one to fifteen carbons,

(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,

(iv) alkoxy of one to fifteen carbons,

(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(vi) thioalkoxy of one to fifteen carbons,

(vii) perfluoroalkyl of one to fifteen carbons,

(viii) perfluoroalkoxy of one to fifteen carbons,

(ix) $-N_3$,

(x) $-NO_2$,

(xi) -CN,

(xii) -OH,

provided that no two -OH groups are attached to the same carbon,

(xiii) -OG,

(xiv) cycloalkyl of three to fifteen carbons,

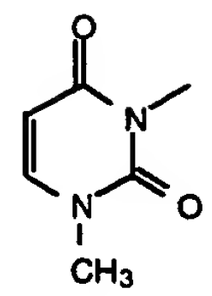
(xv) halo,

(xvi) $-CO_2R_6$,

(xvii) $-L_1NR_7R_8$,

(xviii) $-L_2R_9$,

provided that at least one of R_{13} and R_{14} is other than hydrogen, or



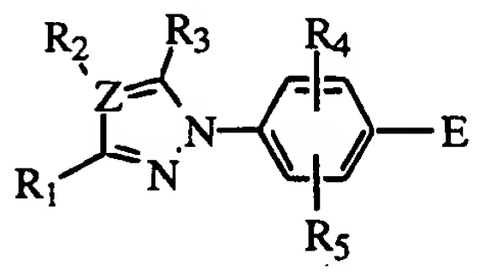
(m)

where (a)-(m) can be optionally substituted with 1, 2, 3, 4, or 5 substituents selected from

halo and

$-L_2R_9$.

2. A compound according to Claim 1 of Formula



,

or a pharmaceutically acceptable salt or prodrug thereof, where

Z is carbon, $\mathbf{R_2}$ is hydrogen, and $\mathbf{R_1}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, and **E** are defined above.

3. A compound according to Claim 2 where $\mathbf{R_1}$ is perfluoroalkyl of one to fifteen carbons and $\mathbf{R_4}$ and $\mathbf{R_5}$ are hydrogen.

4. A compound according to Claim 3 where L_3 is $-N(R_7)C(X)-$, R_7 is hydrogen, and W is O.

5. A compound according to Claim 4 selected from

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-cyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2,3,3-tetramethylcyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2-dichloro-1-methylcyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-oxo-6-pentyl-2H-pyran-3-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyclohexene-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methylcyclopropane-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-2-thiophene-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(1H-pyrrol-1-yl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-7-methoxy-2-benzofuran-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(hydroxymethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-cyanoacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-cyclohexane-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylcyclohexane-carboxamide,

(R)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methoxy-α-(trifluoromethyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]heptanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenoxybenzamide,

3-Amino-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-Amino-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-Azido-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-thiopheneacetamide,

N-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-tricyclo[3.3.1.1^{3,7}]-decanecarboxmide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N^2-[(1,1-dimethylethoxy)-carbonyl]-L-asparagine, phenylmethyl ester,

1,1-dimethylethyl [7-[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(methylthio)propanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-naphthylenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide,

(trans)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenyl-cyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-iodobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-methyl-1,2-benzene-dicarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-pyridinecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chloro-2-nitrobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cinnolinecarboxamide,
4-acetyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,
1,1-dimethylethyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-amino]carbonyl]-1-piperidinecarboxylate,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyridinecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(diethylamino)benzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopentanecarboxmide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclohexanecarboxmide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-piperidinecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(methylsulfonyl)benzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(trifluoromethyl)benzamide,
methyl 3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-carbonyl]benzoate,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chlorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-thiophenecarboxamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,4-benzenedicarboxamide ,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,5-dinitrobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-difluorobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-nitrobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyanobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,3-benzenedicarboxamide ,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-nitrobenzamide,
3-(aminosulfonyl)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,
methyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-carbonyl]benzoate,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxybenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-bromobenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methoxybenzamide,
N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-fluorobenzamide,

(E)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(2-thienyl)-2-propenamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]pyazinecarboxamide,

1,1-dimethylethyl [[4-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-4-oxobutyl]carbamate,

1-acetyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-piperidine-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]butanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chloro-2-methoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methyl-4-(2-thienylcarbonyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methyl-4-(2-thienylcarbonyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methoxy-4-(methythio)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-hydroxy-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,4-dihydroxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-hydroxy-6-methoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-bis(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-4-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-bromo-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-(methylsulfonyl)-benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-dichlorobenzamide,

N-4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl-2,4-dichloro-3,5-dinitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,5,6-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3,4,5-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-bromo-2,3,5,6-tetrafluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-2-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-thiophene-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyrrolidinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-3-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-pyridine-carboxamide,

1,1-dimethylethyl 2-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-amino]carbonyl]-1-pyrrolidinecarboxylate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-nitro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-1H-pyrrole-2-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-6-chloro-3-pyridine-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-bromo-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methyl-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-chloro-2-thiophene-carboxamide,

(S)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-5-oxo-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-oxo-2-pyrrolidine-carboxamide,

N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,
N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide,
N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,
N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2,3,5-trifluorobenzamide,
2-fluoro-N-(4-(5-(2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,
2-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,
2-fluoro-N-(4-(5-(3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,
3-fluoro-N-(4-(5-(2-thienyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
2-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,
N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,
N-(4-(5-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,
2-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide,
2-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)nicotinamide,
N-(4-(5-ethoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,
3-fluoro-N-(4-(5-(methylsulfanyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
3-fluoro-N-(4-(5-methoxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,
N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,
N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,
2-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,
N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

9. A compound according to Claim 8 selected from

ethyl 3-[[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-amino]carbonyl]-amino]benzoate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-cyanophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-fluorophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-[4-(trifluoromethyl)-phenyl]urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3,5-dimethylphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-phenylurea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-chloro-2-methyl-phenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-[4-(butyloxyphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-methyl-3-nitro-phenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(2-chloro-4-nitro-phenyl)urea,

N-(4-acetylphenyl)-N'-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-phenyl]urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-methyl-2-nitro-phenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-bromo-2,6-dimethy-lphenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-heptylurea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-chloro-2-nitro-phenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-2-methyl-5-nitro-phenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-bromo-2-methyl-phenyl)urea,

and

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-chloro-3-nitro-phenyl)urea.

10. A compound according to Claim 3 where L_3 is $-NR_7S(O)_t-$, t is 2, and

17. A compound according to Claim 16 selected from
4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-fluorophenyl)benzenemethanamine,
3-[4-[[[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile,
4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,4-difluorophenyl)benzene-
methanamine,
and
3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile.

18. A compound according to Claim 3 where L_3 is -C(H)=N-.

19. A compound according to Claim 18 that is
(E)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenylmethylene]-2,4-
difluorobenzenamine.

20. A compound according to Claim 3 where L_3 is alkenylene of two to six carbons in the Z or E configuration.

21. A compound according to Claim 20 selected from
(E)-3-[2-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]ethenyl]benzonitrile,
(Z)-3-[2-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]ethenyl]benzonitrile,
and
(E)-1-[4-[2-(2-chlorophenyl)ethenyl]phenyl]-3,5-bis(trifluoromethyl)-1H-pyrazole.

22. A compound according to Claim 2 where
Z is carbon, $\mathbf{R_2}$ is hydrogen, and $\mathbf{R_1}$, $\mathbf{R_3}$, and **E** are defined above,
and
$\mathbf{R_4}$ and $\mathbf{R_5}$ are independently selected from
(1) hydrogen,
(2) alkyl of one to fifteen carbons,
(3) alkoxy of one to fifteen carbons,
(4) halo,
(5) perfluoroalkyl of one to fifteen carbons,
(6) $-CO_2R_6$,
(7) substituted heterocycle,

4-methyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide, and

3,5-dimethyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-isoxazolecarboxamide.

26. A compound according to Claim 2 where
R_1 is hydrogen and R_3 is alkyl of one to fifteen carbons.

27. A compound according to Claim 26 selected from
4-chloro-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]benzamide,
4-methyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-1,2,3-thiadiazole-5-carboxamide, and
3,5-dimethyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-4-isoxazolecarboxamide.

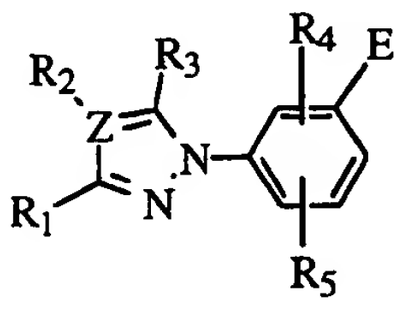
28. A compound according to Claim 2 where
R_1 is perfluoroalkyl of one to fifteen carbons and R_3 is hydrogen;

29. A compound according to Claim 28 that is
3,5-dimethyl-N-[4-[3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]-4-isoxazole-carboxamide.

30. A compound according to Claim 2 where
R_1 is perfluoroalkyl of one to fifteen carbons and R_3 is hydroxyl;

31. A compound according to Claim 30 that is
N-[4-[5-hydroxy-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide.

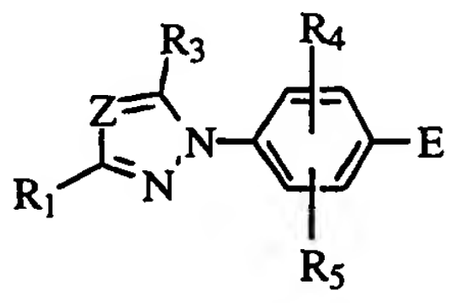
32. A compound according to Claim 1 of formula



,

37. A compound according to Claim 36 selected from
N-[2-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-5-pyridinyl]-2-chlorobenzamide,
N-[2-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-5-pyridinyl]-3-cyanobenzamide,
N-[2-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-5-pyridinyl]-2-chloro-4,5-difluoro-benzamide,
N-(6-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-3-pyridinyl)-2-fluorobenzamide, and
N-(5-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-2-pyridinyl)-2-fluorobenzamide.

38. A compound according to Claim 1 of formula



or a pharmaceutically acceptable salt or prodrug thereof, where
Z is nitrogen, and $\mathbf{R_1}$, $\mathbf{R_3}$, $\mathbf{R_4}$, $\mathbf{R_5}$, and **E** are defined above.

39. A compound according to Claim 38 selected from
3,5-dimethyl-N-[4-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)phenyl]-4-isoxazolecarboxamide and
N-[4-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide.

40. A compound according to Claim 2 where R_1 is -L_2-heterocycle, and the heterocycle can be optionally substituted.

41. A compound according to Claim 40 selected from the group consisting of
3-fluoro-N-(4-(3-(4-pyridinyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,
N-(4-(5-(difluoromethyl)-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,
N-(4-(5-cyano-3-(2-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

42. A compound selected from

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2,3,3-tetramethylcyclopropane-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,2-dichloro-1-methylcyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-oxo-6-pentyl-2H-pyran-3-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,5-difluorobenzenesulfonamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-cyclohexene-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methylcyclopropanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-(3,5-dichlorophenoxy)-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-2-cyclohexene-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-cyclopentene-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methoxycyclohexane-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-butynamide,

ethyl 3-[[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]-amino]benzoate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methyl-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(3-cyanophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-hydroxycyclopropanecarboxamide,

N-[4[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cycloheptanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-benzofurancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-fluoro-1H-indole-2-carboxamide,

(E)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(2-chlorophenyl)-2-propenamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(1H-pyrrol-1-yl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-heptylurea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-(4-chloro-2-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-7-methoxy-2-benzofurancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-2-methyl-5-nitrophenyl)urea,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(hydroxymethyl)-benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-cyanoacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-cyclohexane-1-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylcyclohexanecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-α-methoxy-α-(trifluoromethyl)benzeneacetamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]heptanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenoxybenzamide,

3-amino-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-amino-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-azido-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-thiopheneacetamide,

N-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-tricyclo[3.3.1.1^{3,7}]decane-carboxmide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N^2-[(1,1-dimethylethoxy)-carbonyl]-l-asparagine, phenylmethyl ester,

1,1-dimethylethyl [7-[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-7-oxoheptyl]carbamate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(methylthio)propanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-naphthylenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide,

trans-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-phenylcyclopropane-carboxamide,

3-[4-[[[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]methyl]amino]benzonitrile,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methylbenzamide,

(E)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenylmethylene]-2,4-difluoro-benzenamine,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-4-dimethoxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]cyclopentanepropanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylbenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(trifluoromethyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methyl-2-butenamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-hydroxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-hydroxybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-dimethyl-5-thiazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(hydroxymethyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,4-difluorophenyl)benzenemethanamine,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-(methylsulfonyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-iodobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-heptybenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N'-methyl-1,2-benzenedicarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chloro-2-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cinnolinecarboxamide,

4-acetyl-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

1,1-dimethylethyl 4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-amino]carbonyl]-1-piperidinecarboxylate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-dichloro-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-6-methyl-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-γ-oxobenzenebutanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3,4-tetrahydro-2-naphthalenecarboxamide,

(E)-1-[4-[2-(2-chlorophenyl)ethenyl]phenyl]-3,5-bis(trifluoromethyl)-1H-pyrazole,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(4-chlorophenoxy)-2-methylpropanamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]acetamide,

4-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoic acid,

phenylmethyl N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]-4-oxobutyl]carbamate,

3-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]benzoic acid,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-bromo-2-thiophenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methyl-2-thiophenecarboxamide,

2-amino-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluoro-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloro-4-(methylsulfonyl)-
2-thiophenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1H-pyrrole-2-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,6-dichloro-2-pyridinecarboxamide

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-(2-nitrophenoxy)acetamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-cyanophenyl)benzamide,

4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-pyridinyl)benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-(trifluoromethyl)benzamide,

N-[2-(aminocarbonyl)phenyl]-4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]benzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-chlorobenzeneacetamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-dichlorobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-5-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluoro-2-(trifluoromethyl)-benzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-fluorobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-difluorobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-cyanobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-bromo-3-nitrobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-fluoro-benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-(methylsulfonyl)-benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-dichlorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-difluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloro-4-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,5-difluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-6-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-fluoro-6-(trifluoromethyl)-benzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-chloro-2-fluorobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methyl-2-nitrobenzamide,

N-[3-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-cyanobenzamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-thiophenecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-pyrrolidinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-3-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-chloro-4-pyridinecarboxamide,

1,1-dimethylethyl 2-[[[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]amino]carbonyl]-1-pyrrolidinecarboxylate,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-nitro-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-1H-pyrrole-2-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-6-chloro-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-bromo-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-methyl-2-furancarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-chloro-2-thiophenecarboxamide,

(S)-N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]tetrahydro-5-oxo-2-furan-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-oxo-2-pyrrolidinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-bromo-3-pyridinecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-nitro-3-thiophene-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-(trifluoromethyl)phenyl]-3,5-dimethyl-4-isoxazolecarboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-methylphenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-[4-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]-2-methoxyphenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

4-chloro-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]benzamide,

4-methyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadiazole-5-carboxamide,

3,5-dimethyl-N-[4-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-isoxazolecarboxamide,

4-chloro-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]benzamide,

4-methyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-1,2,3-thiadiazole-5-carboxamide,

3,5-dimethyl-N-[4-(5-methyl-1H-pyrazol-1-yl)phenyl]-4-isoxazolecarboxamide,

3,5-dimethyl-N-[4-[3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]-4-isoxazolecarboxamide,

N-[4-[5-hydroxy-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-[4-[5-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1,2,3-thiadoazole-5-carboxamide,

3-amino-N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-chloro-5-methoxyisonicotinamide,

N-(6-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-3-pyridinyl)-2-fluorobenzamide,

methyl 2-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-5-((2-fluorobenzoyl)amino)benzoate,

4-(aminomethyl)-N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-chlorobenzamide,

N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-methylacrylamide,

N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-chloro-2-fluorobenzamide,

N-(5-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-2-pyridinyl)-2-fluorobenzamide,

N-(3-amino-4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide, N-(4-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)-3-cyanophenyl)-2-fluorobenzamide,

N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluoronicotinamide,

2-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

3-fluoro-N-(4-(5-nitro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

N-(4-(5-chloro-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)phenyl)-3-fluoroisonicotinamide,

3-fluoro-N-(4-(5-(1-methyl-1H-pyrrol-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

3-chloro-N-(4-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2,3-difluorobenzamide,

N-(4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-3-chloroisonicotinamide,

2-chloro-N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,

3-chloro-N-(4-(5-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2-fluorobenzamide,

2-chloro-N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)benzamide,

N-(4-(5-(difluoromethoxy)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)-2,3-difluorobenzamide,

3-fluoro-N-(4-(3-(4-pyridinyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

N-(4-(5-(difluoromethyl)-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

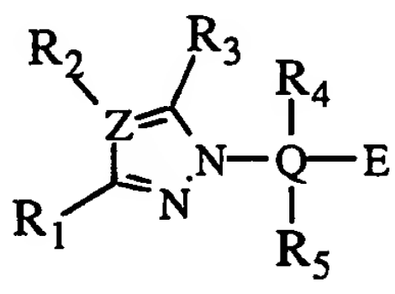
N-(4-(5-cyano-3-(2-pyridinyl)-1H-pyrazol-1-yl)phenyl)-3-fluoroisonicotinamide,

N-(4-(5-cyano-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)-4-methyl-1,2,3-thiadiazole-5-carboxamide,

3-fluoro-N-(4-(5-nitro-3-(3-pyridinyl)-1H-pyrazol-1-yl)phenyl)isonicotinamide,

43. A method of inhibiting interleukin-2, interleukin-4, and interleukin-5 production in a mammal comprising adminstering a therapeutically effective amount of a compound of Claim 1.

44. A method of treating immunologically-mediated diseases in a mammal comprising administering a therapeutically effective amount of a compound of Formula **I**



I

or a pharmaceutically acceptable salt or prodrug thereof, where $\mathbf{R_1}$ and $\mathbf{R_3}$ are independently selected from

(1) hydrogen,

(2) aryl,

(3) perfluoroalkyl of one to fifteen carbons,

(4) halo,

(5) -CN,

(6) $-NO_2$,

(7) -OH,

(8) -OG where G is a hydroxyl protecting group,

(9) $-CO_2R_6$ where R_6 is selected from

(a) hydrogen,

(b) cycloalkyl of three to twelve carbons,

(c) aryl,

(d) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkyl of one to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) thioalkoxy of one to fifteen carbons,

(iv) halo,

(v) $-NO_2$, and

(vi) $-N_3$,

is substituted with 1 or 2 substituents selected from the group consisting of aryl,

(e) cycloalkyl of three to twelve carbons,

(f) aryl,

(g) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from

(i) alkyl of one to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) thioalkoxy of one to fifteen carbons,

(iv) halo,

(v) $-NO_2$, and

(vi) $-N_3$,

(h) $-OR_6$,

provided that only one of R_7 or R_8 is $-OR_6$,

(i) a nitrogen protecting group,

(j) alkyl of one to fifteen carbons,

(k) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkoxy of one to fifteen carbons,

(ii) thioalkoxy of one to fifteen carbons,

(iii) aryl,

(iv) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from

alkyl of one to fifteen carbons,

alkoxy of one to fifteen carbons,

thioalkoxy of one to fifteen carbons,

halo,

$-NO_2$, and

$-N_3$,

(v) cycloalkyl of three to fifteen carbons,

(vi) halo,

(vii) $-CO_2R_6$, and

(viii) -OH,

(l) alkenyl of three to fifteen carbons,

(vi) $-N_3$,

(d) alkyl of one to fifteen carbons,

(e) heterocycle,

(f) alkenyl of two to fifteen carbons, and

(e) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkenyl of two to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) -CN,

(iv) $-CO_2R_6$,

(v) -OH,

provided that no two -OH groups are attached to the same carbon,

(vi) thioalkoxy of one to fifteen carbons,

(vii) alkynyl of two to fifteen carbons,

(viii) aryl,

(ix) aryl substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,
$-NO_2$, and
$-N_3$,

(x) cycloalkyl of three to twelve carbons, and

(xi) halo,

(xii) $-NR_7R_8$,

(xiii) heterocycle, and

(xiv) heterocycle substituted with 1, 2, or 3, or 4 substituents independently selected from
alkyl of one to fifteen carbons,
alkoxy of one to fifteen carbons,
thioalkoxy of one to fifteen carbons,
halo,

(a) hydrogen and

(b) alkyl of one to fifteen carbons,

(19) $-C(=NR_X)NR_YR_Z$,

(20) $-NR_XC(=NR_{X'})NR_YR_Z$ where R_X, R_Y and R_Z are defined previously and $R_{X'}$ is selected from

(a) hydrogen and

(b) alkyl of one to fifteen carbons,

(21) $-NR_XC(O)OR_W$, where R_W is selected from

(a) alkyl of one to fifteen carbons and

(b) alkenyl of three to fifteen carbons,

provided that a carbon of a carbon-carbon double bond is not attached directly to oxygen, and

(22) $-OC(O)NR_7R_8$;

Z is nitrogen or carbon;

R_2 is absent or is selected from

(1) hydrogen,

(2) $-CO_2R_6$,

(3) alkyl of one to fifteen carbons,

(4) $-C(O)R_{6'}$ where $R_{6'}$ is selected from

(a) alkyl of one to fifteen carbons,

(b) aryl, and

(c) heterocycle,

(5) $-C(O)NR_{7'}R_{8'}$ where $R_{7'}$ and $R_{8'}$ are independently selected from

(a) hydrogen,

(b) alkyl of one to fifteen carbons, or

$R_{7'}$ and $R_{8'}$ together with the nitrogen to which they are attached form a ring selected from

(i) piperidine,

(ii) piperazine,

(iii) morpholine,

(iv) thiomorpholine, and

(v) thiomorpholine sulfone

(13) $-C(=NR_6)NR_7R_8$,

(14) $-NR_{12}(=NR_6)NR_7R_8$ where R_6, R_7, and R_8 are defined previously and R_{12} is selected from

(a) hydrogen,

(b) cycloalkyl of three to twelve carbons,

(c) aryl,

(d) alkyl of one to fifteen carbons, and

(e) alkyl of one to fifteen carbons substituted with 1, 2, or 3, or 4 substituents independently selected from

(i) alkenyl of two to fifteen carbons,

(ii) alkoxy of one to fifteen carbons,

(iii) thioalkoxy of one to fifteen carbons,

(iv) alkynyl of two to fifteen carbons, and

(v) aryl,

(15) $-L_2$-heterocycle, and

(16) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3, or 4 substituents independently selected from

(a) alkyl of one to fifteen carbons,

(b) perfluoroalkyl of one to fifteen carbons,

(c) alkoxy of one to fifteen carbons,

(d) thioalkoxy of one to fifteen carbons,

(e) halo,

(f) $-N_3$, and

(g) $-NO_2$;

E is

(1) $-L_3$-B where L_3 is selected from

(a) a covalent bond,

(b) alkenylene of two to six carbons in the Z or E configuration,

(c) alkynylene of two to six carbons,

(d) -C(X)-,

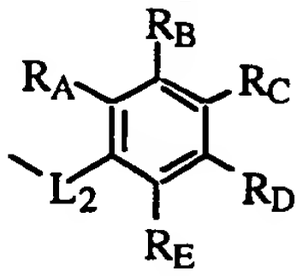
(e) -N=N-,

(f) $-NR_7$-,

(g) $-N(R_7)C(O)N(R_8)$-,

attached to L_3 when L_3 is other than a covalent bond

where (a), (b) and (c), can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(i)  where L_2 is defined previously and R_A, R_B, R_C, R_D, and R_E are independently selected from

hydrogen,

alkanoyl where the alkyl part is one to fifteen carbons,

alkanoyloxy where the alkyl part is one to fifteen carbons,

alkoxy of one to fifteen carbons,

thioalkoxy of one to fifteen carbons,

alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo ,

perfluoroalkyl of one to fifteen carbons,

perfluoroalkoxy of one to fifteen carbons,

$-N_3$,

$-NO_2$,

-CN,

-OH,

-OG,

cycloalkyl of three to fifteen carbons,

halo,

$-CO_2R_6$

$-L_1NR_7R_8$

$-L_2R_9$

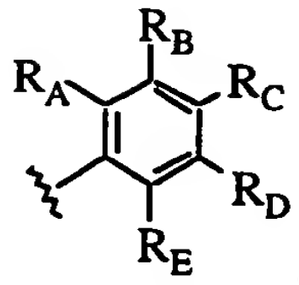
alkyl of one to fifteen carbons,

alkyl of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents independently selected from (=X),

alkanoyloxy where the alkyl part is one to fifteen

(iv) alkoxy of one to fifteen carbons,
(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,
(vi) thioalkoxy of one to fifteen carbons,
(vii) perfluoroalkoxy of one to fifteen carbons,
(viii) $-N_3$,
(ix) $-NO_2$,
(x) -CN,
(xi) -OH,
provided that no two -OH groups are attached to the same carbon,
(xii) -OG,
(xiii) cycloalkyl of three to fifteen carbons,
(xiv) halo,
(xv) $-CO_2R_6$,
(xvi) $-L_1NR_7R_8$,
(xvii) perfluoroalkyl of one to fifteen carbons,
(xviii) $-L_2$-heterocycle, and
(xix) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3, or 4 substituents independently selected from
(=X),
alkanoyl where the alkyl part is one to fifteen carbons,
alkanoyloxy where the alkyl part is one to fifteen carbons,
alkoxy of one to fifteen carbons,
alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo ,
thioalkoxy of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
perfluoroalkoxy of one to fifteen carbons,
$-N_3$,
$-NO_2$,
-CN,

-N_3,

(f)  ,

provided that when R_1 and R_3 are both perfluoroalkyl of one carbon, Z is carbon, R_2 is hydrogen, Q is phenyl that is 4-substituted by E relative to the position of attachment of the pyrazole ring to the phenyl group, R_4 and R_5 are hydrogen, E is -L_3-B, L_3 is -$N(R_7)C(X)$-, R_7 is hydrogen, X is oxygen, and R_A, R_B, R_D, and R_E are hydrogen, R_C is other than chloro, and

(g) heterocycle where the heterocycle can be optionally substituted with 1, 2, 3, or 4 substituents independently selected from

(i) (=X),

(ii) alkanoyl where the alkyl part is one to fifteen carbons,

(iii) alkanoyloxy where the alkyl part is one to fifteen carbons,

(iv) alkoxy of one to fifteen carbons,

(v) alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,

(vi) halo ,

(vii) thioalkoxy of one to fifteen carbons,

(viii) perfluoroalkyl of one to fifteen carbons,

(ix) perfluoroalkoxy of one to fifteen carbons,

(x) -N_3,

(xi) -NO_2,

(xii) -CN,

(xiii) -OH,

provided that no two -OH groups are attached to the same carbon,

(xiv) -OG,

(xv) cycloalkyl of three to fifteen carbons,

(xvi) halo,

(xii) -OG,
(xiii) cycloalkyl of three to fifteen carbons,
(xiv) halo,
(xv) $-CO_2R_6$,
(xvi) $-L_1NR_7R_8$,
(xvii) perfluoroalkyl of one to fifteen carbons,
(xviii) $-L_2$-heterocycle, and
(xix) $-L_2$-heterocycle where the heterocycle is substituted with 1, 2, 3,or 4 substituents independently selected from
(=X),
alkanoyl where the alkyl part is one to fifteen carbons,
alkanoyloxy where the alkyl part is one to fifteen carbons,
alkoxy of one to fifteen carbons,
alkoxy of one to fifteen carbons substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halo,
thioalkoxy of one to fifteen carbons,
perfluoroalkyl of one to fifteen carbons,
perfluoroalkoxy of one to fifteen carbons,
$-N_3$,
$-NO_2$,
-CN,
-OH,
provided that no two -OH groups are attached to the same carbon,
-OG,
cycloalkyl of three to fifteen carbons,
halo,
$-CO_2R_6$,
$-L_1NR_7R_8$,
$-L_2R_9$,

(e) cycloalkyl of three to twelve carbons,
(f) cycloalkenyl of four to twelve carbons,

(vii) perfluoroalkyl of one to fifteen carbons,

(viii) perfluoroalkoxy of one to fifteen carbons,

(ix) $-N_3$,

(x) $-NO_2$,

(xi) -CN,

(xii) -OH,

provided that no two -OH groups are attached to the same carbon,

(xiii) -OG,

(xiv) cycloalkyl of three to fifteen carbons,

(xv) halo,

(xvi) $-CO_2R_6$,

(xvii) $-L_1NR_7R_8$,

(xviii) $-L_2R_9$,

provided that at least one of R_{13} and R_{14} is other than hydrogen, or R_{13} and R_{14} together with the nitrogen to which they are attached form a ring selected from

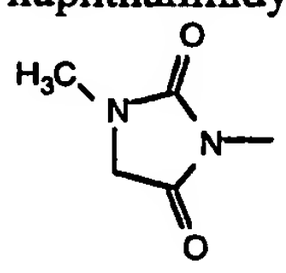
(a) succinimidyl,

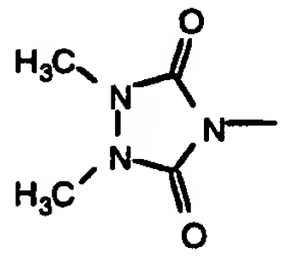
(b) maleimidyl,

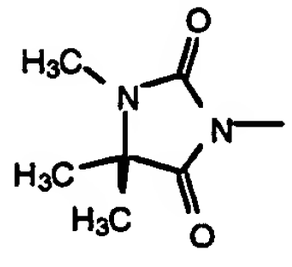
(c) glutarimidyl,

(d) phthalimidyl,

(e) naphthalimidyl,

(f)  ,

(g)  ,

(h)  ,

INTERNATIONAL SEARCH REPORT

I. national Application No
PCT/US 99/07766

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/16 A61K31/475 A61K31/42 A61K31/425 A61K31/44
A61K31/445 A61K31/415 C07D405/10 C07D403/10 C07D495/04
C07D409/10 C07D417/10 C07D401/10 C07D413/10 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TSUJI, KIYOSHI ET AL: "Studies on anti-inflammatory agents. V. Synthesis and pharmacological properties of 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-'4-(methylsulfinyl)phenyl!pyrazole and related compounds" CHEM. PHARM. BULL. (1997), 45(9), 1475-1481 , XP002112607 abstract page 1476 page 1477; tables 1,2 --- -/--	1,43,44

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 1999	03/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

	International Application No PCT/US 99/07766

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 33751 A (SANOFI WINTHROP, INC., USA) 1995 abstract; claims 1,21,28 examples 4-10,12,20,24,25	1,43,44
A	WO 95 15317 A (G.D. SEARLE & CO., USA) 1994 abstract; claims 1,15 page 35; example 1	1,43,44
A	WO 92 01684 A (PFIZER INC., USA) 1991 abstract; claims page 38 - page 43; examples	1,43,44
A	US 5 585 357 A (DOLLE, ROLAND E. ET AL) 1996 abstract; claims 1,9,17; example 1	1,43,44
A	EP 0 644 198 A (STERLING WINTHROP INC., USA) 1994 abstract; claims 2,15; example 1	1,43,44
E	WO 99 23091 A (BOEHRINGER INGELHEIM PHARMACEUTICALS, INC., USA) 1998 abstract; claims page 51 - page 58; examples 2,4-43; table I	1,43,44
E	WO 99 19303 A (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 1998 abstract page 35 - page 41; tables 2-5	1

1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-111, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by the examples and claims 2, 32, 34, 38 and 42.
The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/07766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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